2018

Earle A. Chiles Research Institute 2017 Year In Review

Earle A. Chiles Research Institute

2017 YEAR IN REVIEW

Earle A. Chiles Research Institute

A DIVISION OF PROVIDENCE CANCER INSTITUTE
AT THE ROBERT W. FRANZ CANCER CENTER

DAVID FERRIDAY: husband, father, soccer competitor, cancer survivor.

EARLE A. CHILES
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Cancer Institute

2017 YEAR IN REVIEW

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For David Ferriday, diagnosed with stage III colon cancer, a new immunotherapy clinical trial at Providence was his game-changer. *See Page 4.*

EARLE A. CHILES RESEARCH INSTITUTE

A leader in cancer immunotherapy research and innovation since 1993, the Earle A. Chiles Research Institute is a world-class research facility, and home to a team of internationally known scientists and physicians.

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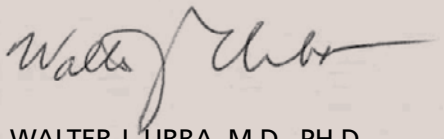


WALTER J. URBA, M.D., PH.D.

Member, director and endowed chair of Cancer Research,
Earle A. Chiles Research Institute,
a division of Providence Cancer Institute
at the Robert W. Franz Cancer Center

MESSAGE FROM THE DIRECTOR

Welcome to our 2017 Year in Review, the accomplishments report of the Earle A. Chiles Research Institute.

We are pleased to share with you our highlights from an exciting year in cancer medicine and research. 2017 marked the 30-year anniversary of our institute. From our humble beginnings, our team has grown to more than 130 investigators and research personnel, including 19 faculty members recognized globally for their pioneering contributions to cancer immunotherapy.

With the passing of another year, we find yet again that a novel immunotherapy – adoptive cell therapy – is named the Advance of the Year by the American Society of Clinical Oncology. Through the development of our adoptive cell therapy and genomics programs, we are poised to offer genome-guided, personalized immunotherapies to our patients.

Another important advancement of last year came with the first approval by the Food and Drug Administration for a cancer therapy based not on tumor type or location, but on a shared genetic profile. This immunotherapy – from which an estimated 60,000 cancer patients stand to benefit each year – may represent a new standard of care, and we are proud of our contributions to the revolutionary clinical trial which prompted the accelerated FDA approval.

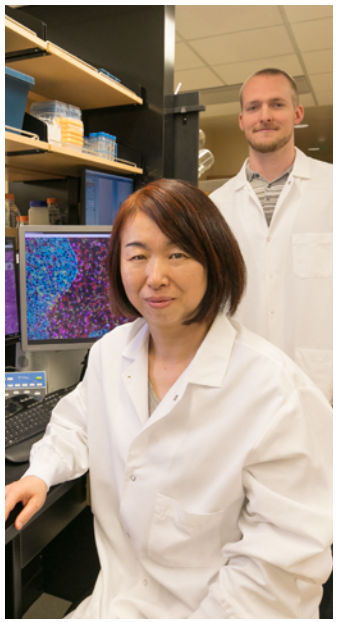
2017 was also a year of transformation for Providence Cancer Center brought about by philanthropic support. In tribute to our longtime friend and benefactor, the center was renamed the Robert W. Franz Cancer Center. As a former board member of Providence Portland Medical Foundation, Bob gave generously of his time and resources to support our growing cancer program. Together with his sister, Elsie Franz Finley, he was instrumental to our evolution as a worldwide leader in cancer immunotherapy.

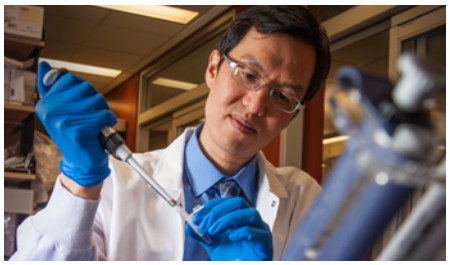
The Robert W. Franz Cancer Center is now part of Providence Cancer Institute – a regional ministry supporting the comprehensive cancer services of Providence Health & Services throughout Oregon. And as we plan for the future, construction is underway to ensure we are equipped for state-of-the-art care and translational research for many years to come.

When I reflect on our journey over the past three decades, I am filled with gratitude for the many friends and supporters who have joined us along the way. And memories of those who have passed away remind us that our job is not done.

Cancer does not quit, and neither do we. I invite you to join us on our quest for a cancer-free future. With your support, together we can finish cancer.

NEW ADDITIONS AND NOTEWORTHY ACHIEVEMENTS





From left, Immuno-Histology Core, Antitumor T-cell Response Lab, and genomics team. At right, Todd S. Crocenzi, M.D.

Immuno-Histology Core

The application of immunohistochemistry to preclinical and clinical research is critical to elucidating the mechanisms of cancer immunotherapy. At the forefront of this technology, **Zhaoyu Sun, Ph.D.**, manager, Immuno-Histology Core, advises our investigators on imaging techniques to accomplish their research goals. With expertise in immunohistology, quantitative image analysis and multiplex immunofluorescence staining, she oversees the incorporation of new antibodies for investigation, the evaluation of new methods and techniques, and quality control. Established in 2017, the core is one of two components of the Immune Monitoring Laboratory directed by Associate Member William L. Redmond, Ph.D. *Learn more on Page 38.*

Adoptive cell therapy lab

A sought-after recruit from the National Cancer Institute, **Eric Tran, Ph.D.**, assistant member, Antitumor T-cell Response Laboratory, joined our faculty in 2017 to lead a laboratory devoted to adoptive cell therapy – a highly personalized immunotherapy approach celebrated as the Advance of the Year by the American Society of Clinical Oncology. Dr. Tran trained under renowned physician scientist Steven A. Rosenberg, M.D., Ph.D., chief of the NCI Surgery Branch, with whom he contributed to groundbreaking studies showing the effectiveness of this treatment strategy in patients with cancer. *Learn more on Page 6.*

Genomics expansion

Precision oncology – personalized cancer care aided by genomic profiling – is a promising treatment strategy for patients with cancer. By analyzing the genetic profiles of patients' individual tumors, clinicians may be able to predict which therapies will offer the greatest benefits. In 2017, we expanded our genomics program to complement our steadfast integration of genomics and immunotherapy. Computational and systems biologist **Brady Bernard, Ph.D.**, and genomic scientist **Brian Piening, Ph.D.**, join Carlo B. Bifulco, M.D., our director of Translational Molecular Pathology, in developing robust bioinformatics and genomics support for our investigators. *Learn more on Page 26.*

New standard of care

A phase II clinical trial drew national headlines in 2017 when 66 of 86 patients with cancer saw their tumors shrink or stabilize in response to immunotherapy. For 18 of the patients who responded to therapy, their tumors vanished completely. With nearly 77 percent of patients benefiting from disease control, the study's novel design and notable responses in patients with multiple tumor types captured the interest of researchers across the country.

> These results will likely establish a new standard of care, with the potential for up to 60,000 cancer patients annually to benefit from this treatment approach.

As reported in Science and The New York Times, study investigators found evidence that a checkpoint immunotherapy was effective in treating patients whose cancers shared a distinct genetic abnormality known as mismatch repair deficiency – a defect in the ability to repair damaged DNA, leading to the first instance of approval by the Food and Drug Administration for a cancer treatment based on genetic profile rather than tumor type or origin in the body.

The study, which is ongoing, is led by Johns Hopkins University in collaboration with six institutions across the United States, including the Robert W. Franz Cancer Center. **Todd S. Crocenzi, M.D.**, associate member and director of Gastrointestinal Oncology Research, was the second investigator to enroll patients to the study. "These results will likely establish a new standard of care, with the potential for up to 60,000 cancer patients annually to benefit from this treatment approach," said Dr. Crocenzi. *Learn more on Page 24.*

Center of Hope Initiative

Donors did it! In 2013, Providence Foundations of Oregon launched the Center of Hope Initiative, a five-year, $65 million campaign to support services of Providence Cancer Institute throughout Oregon, including cancer research, patient care and operational priorities. In 2017, we exceeded this goal ahead of schedule thanks to the generosity of donors. The initiative also strengthened our statewide partnerships with community organizations such as Safeway Albertsons, Portland General Electric, Providence Hood to Coast Relay, The Human Bean and Susan G. Komen.

Philanthropic support provides opportunity for growth and aids our sustainability. Gifts have strengthened our endowment, helping us recruit and retain more scientists and physicians. Plans are underway to expand our laboratory space and recruit investigators to lead new areas of cancer research and develop better therapies for patients with cancer.

Philanthropy was also instrumental in establishing Providence Guest House, a 30-room housing facility opened in 2015 for patients and their families who come to Portland for care, and the 11-story expansion of cancer services and research in 2008. In 2017, this facility was renamed the Robert W. Franz Cancer Center to honor the single largest donor in Providence's 142 years in Oregon. *Learn more on Page 42.*

HISTORY MAKERS
30 YEARS OF INNOVATION

Since our founding 30 years ago, we have helped advance both the science of cancer research and the standard of care for patients with cancer. From leading the global clinical trial of ipilimumab to launching Oregon's first adoptive cell therapy lab for patients with epithelial cancers, our team has often been first in the world, or first in Oregon, to offer promising immunotherapies to patients with cancer.

- **1987** — Earle A. Chiles Research Institute is founded
- **1994** — First in Oregon: Adoptive cell therapy for renal cancer
- **1995** — First globally: gene-modified vaccine + adoptive cell therapy for cancer
- **1996** — First in Oregon: gene-modified vaccine for breast cancer
- **2000** — First in Oregon: sipuleucel-T for prostate cancer
- **2004** — First globally: IL-21 for melanoma and renal cancer
- **2006** — First-in-human trial of anti-OX40
- **2008** — First-in-human trial of DRibble vaccine
- **2009** — First-in-human trial of SBRT + IL-2 for melanoma and renal cancer
- **2011** — First cancer immunotherapy, ipilimumab, approved by FDA
- **2012** — First in Oregon: nivolumab for lung cancer
- **2014** — First globally: modified *Listeria* vaccine for glioblastoma
- **2016** — First globally: nivolumab + varlilumab for ovarian cancer
- **2017** — First in Oregon: adoptive cell therapy lab for epithelial cancers
- **2017** — First globally: nivolumab + lirilumab for head and neck cancer

Team Ferriday scores a win over cancer

WHEN DAVID FERRIDAY was working on the 11-story expansion of cancer services at Providence Portland Medical Center, he knew it was a project that could improve the lives of patients with cancer. What the Portland architect could not foresee was the personal significance it would have in his future.

Ferriday's employer, ZGF Architects, was engaged to lead the project. "It was early in my career. My role was limited to working on the inpatient floors with the interior designer," said Ferriday. Opened in 2008, the tower's award-winning design brings together cancer services and research, blending science and care for whole-person healing. From top to bottom, windows and skylights carry natural light to patient rooms and treatment spaces. "The public areas we provided outside of the patient rooms resemble living rooms, with nice views for patients and their families," said Ferriday. "I can't say I ever saw myself actually using them."

Routine screening

A decade later, the 50-year-old husband and father of three underwent routine screening for colon cancer. An avid soccer player, Ferriday was in excellent health. When the colonoscopy revealed he had locally advanced cancer – stage III out of IV stages, he was stunned. Scans showed a 7-centimeter tumor wrapped around the inside of his colon and the invasion of nearby lymph nodes.

Although deaths from colorectal cancer have dropped steadily in recent decades, the disease remains one of the most lethal forms of cancer with fewer than 65 percent of patients surviving beyond five years. In 2017, an estimated 140,000 people were newly diagnosed, and more than 50,000 died from the disease.

"My care has been top notch at every step."

Ferriday's primary care doctor referred him to Providence. A patient of the cancer center he once helped design, Ferriday met Medical Oncologist Anupama Acheson, M.D. She recommended the standard of care – chemotherapy and radiation as an attempt to shrink the tumor, followed by surgery. She also offered Ferriday the chance to participate in an immunotherapy clinical trial designed for patients like him, one that was available only at Providence.

Putting cancer on the defensive

Physician scientist Kristina H. Young, M.D., Ph.D., has studied the effects of radiation and immunotherapy in colorectal cancer for more than a decade. After completing her medical and doctoral training in Oregon, the California native remained to pursue a fellowship in translational radiation oncology at the Earle A. Chiles Research Institute. In 2015, she joined its faculty to lead her own laboratory, making Portland her home. The following year she opened a phase II clinical trial testing galunisertib, an experimental immunotherapy given as an immune-boosting treatment prior to standard care, in patients with stage II or higher colorectal cancer.

Galunisertib attacks cancer at multiple levels, from mechanisms involved in cancer cell growth to the reinforcement of patients' anti-cancer immune responses. With standard care, a mere 10 percent of patients experience complete regression of their tumors. By adding galunisertib before radiation and chemotherapy, Dr. Young hoped the therapeutic trifecta would help more patients respond to therapy.

For Ferriday, the timing and location could not have been better. Dr. Young's study is the first of its kind worldwide. Of 50 patients planned to participate, he was the second to enroll in the study. For two weeks, he took galunisertib daily in the form of a pill. Then he started radiation and chemotherapy. When it came time for surgery, he had completed four weeks of immunotherapy concurrent with chemoradiation, and experienced few side effects.

A winning strategy

A defender on two Portland soccer teams, Ferriday continued playing matches throughout his treatments. "Physically it was hard, but it lifted my spirits immensely to be supported and to just be out there," said Ferriday. Soccer enthusiasm runs deep in his household. His 16-year-old daughter Addie plays central midfield for Lincoln High School, and another daughter rose to play in a semi-professional league.

A native Oregonian, Ferriday grew up in Portland. Like his daughter, he attended Lincoln. That's where he met Sally Tapanen through mutual friends. Years later, they reconnected at a school function, and married soon after. They were still newlyweds when they received his devastating diagnosis. "Thinking you're going to lose your husband – it's indescribable," said Sally. "He tried to not let anything stop him."

With his family rallied around him, Ferriday underwent surgery in February 2017. And what his surgeons found was remarkable: his bulky tumor had shrunk five-fold to 1.4 centimeters, and all his lymph nodes were free of the disease. For Ferriday and his family, Dr. Young's strategy was a success. Surgeons excised the remaining cancer and he was on his way to recovery.

Out on the field, he has a new passion to share. "Because my friends are all hitting the 50-year mark, I am really on them about getting screened for colon cancer," said Ferriday. "I feel so fortunate to have health insurance through Providence. My care has been top notch at every step."

Learn more about Dr. Young and this study on Page 18.

From left, Addie Ferriday, her dad David Ferriday and his wife Sally Tapanen.

Eric Tran, Ph.D., assistant member, Antitumor T-cell Response Laboratory

Antitumor T-cell Response Laboratory

As leader of the Antitumor T-cell Response Laboratory, **Eric Tran, Ph.D.**, is investigating how adoptive cell therapy, or ACT, can be optimized to mediate cancer regression.

For Dr. Tran, 2017 was a year of opportunity. Recruited from the National Cancer Institute where he studied under cancer immunotherapy pioneer Steven A. Rosenberg, M.D., Ph.D., Dr. Tran joined the Earle A. Chiles Research Institute in January and began developing his lab. His newly created team, comprising a postdoctoral fellow and three research associates, is learning the specialized techniques of ACT he mastered while at the NCI. They are developing novel genome-guided T-cell therapies for patients with advanced cancers.

GENOME-GUIDED ACT

A highly personalized form of immunotherapy, ACT harnesses the ability of the immune system to eliminate cancer through the collection, amplification and reinfusion of patients' tumor-killing T cells. Dr. Tran seeks to augment this promising approach with the power of genomics.

In his treatment strategy, patients' tumor samples are obtained by surgical resection, and peripheral blood samples are also collected. T cells known to induce cancer regression are harvested from the samples, and genomic sequencing is performed to identify any DNA mutations in the tumors. Then Dr. Tran's team analyzes the ability of the T cells to recognize the genetic

mutations discovered by genomic sequencing. T cells with the greatest tumor-reactivity are expanded to vast quantities, typically billions, before they are reinfused to patients as highly specialized, anti-cancer armies. After infusion, patients may receive other immunotherapies, such as interleukin-2, which enhance the effectiveness of their T cells.

To perform the genomic sequencing essential to this approach, Dr. Tran is aided by Carlo B. Bifulco, M.D., member and medical director, Molecular Genomics, and the bioinformatics team he oversees. A genetic mutation of particular interest to Dr. Tran is KRAS G12D, a mutation common to multiple cancers which bears potential as a therapeutic target of ACT, as reported by Drs. Rosenberg and Tran in the New England Journal of Medicine.

> A major hurdle facing the field of cancer immunotherapy is to define mechanisms of immune resistance in the tumor microenvironment, and develop strategies to overcome them.

Dr. Tran will also partner with Brendan D. Curti, M.D., member and director, Cytokine and Adoptive Immunotherapy Program, to administer interleukin-2 and other immunotherapies, and with hepatobiliary and pancreatic surgeon Pippa H. Newell, M.D., assistant member and medical director of Providence Liver Cancer Clinic, among other clinicians.

PROOF OF CONCEPT

NCI-supported research provided strong evidence that cancer patients' responses to checkpoint immunotherapy are due in part to their tumor-reactive T cells. Clinical trials conducted by Dr. Tran and colleagues provided direct evidence that ACT can be effective in mediating regression of advanced cancers, with two reports of objective regression in patients with metastatic colorectal cancer and metastatic bile duct cancer.

Despite recent progress, most cancer patients are not cured by current immunotherapy. "A major hurdle facing the field of cancer immunotherapy is to define mechanisms of immune resistance in the tumor microenvironment, and develop strategies to overcome them," said Dr. Tran. As noted in his Nature Immunology article, the immunological targeting of cancer mutations may represent the final common pathway that results in cancer regression in response to a variety of cancer immunotherapies. "Effectively harnessing this pathway holds promise for improving clinical outcomes in patients with metastatic cancers," said Dr. Tran.

In recognition of its potential to change treatment paradigms dramatically, ACT was selected as the Advance of the Year by the American Society of Clinical Oncology. And for the potential impact his research may have to advance cures for cancer, Dr. Tran was chosen among 15 promising early-career scientists by the Sidney Kimmel Foundation, which awarded him a two-year research scholar grant.

FUTURE CLINICAL TRIALS

In collaboration with his colleagues, Dr. Tran is developing clinical trials for patients whose cancers are predicted to recur within three years. These include pancreatic cancer and cholangiocarcinoma, cancers with some of the poorest prognoses. "We hope to offer patients this therapy as early as 2019," said Dr. Tran.

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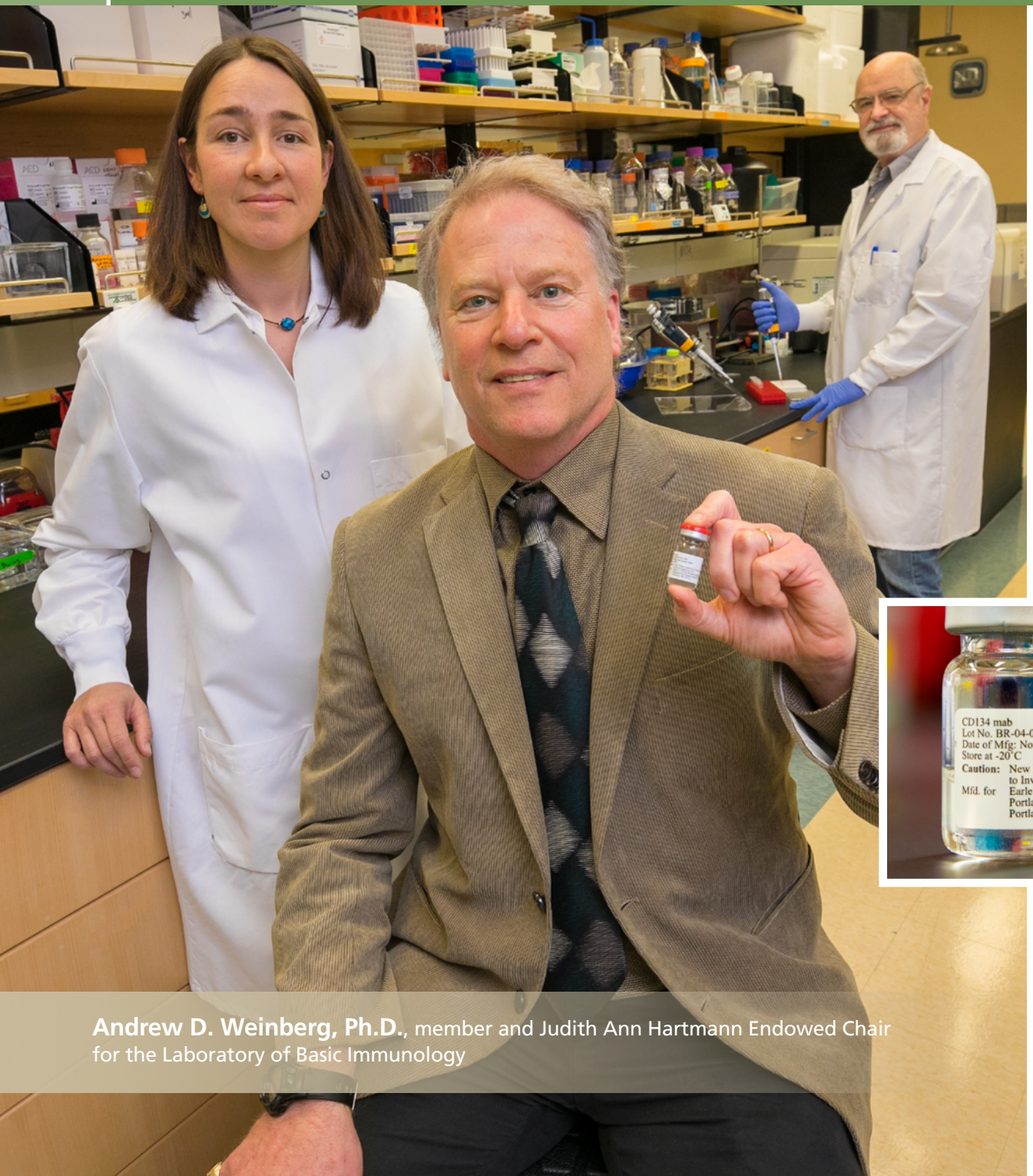

Andrew D. Weinberg, Ph.D., member and Judith Ann Hartmann Endowed Chair for the Laboratory of Basic Immunology

Basic Immunology Laboratory

Andrew D. Weinberg, Ph.D., is a leading expert in the immune-stimulating protein OX40, also known as CD134, and its antibody anti-OX40, an immunotherapy in development for patients with cancer. He is investigating the therapeutic effects of anti-OX40 therapy on a newly identified immune cell population.

Understanding why the immune system fails to eradicate tumors has been a goal of tumor immunologists for decades. One approach to this vexing problem is to identify tumor antigen-specific T cells in cancer patients, and enhance the cells' ability to eliminate cancer. Dr. Weinberg's team took up this strategy, and their findings may have important clinical implications.

TUMOR ANTIGEN-SPECIFIC T CELLS

Antigens are proteins that alert the immune system to the presence of harmful entities such as viruses and tumors. CD8 T cells, a type of T lymphocyte, are capable of recognizing antigens produced by tumor cells – known as tumor antigens, and launching an anti-cancer immune response. However, when confronted with the immune-suppressing forces of the tumor microenvironment, the T cells can be rendered ineffective. Identifying and boosting patients' tumor antigen-specific T cells is an effective treatment strategy, made more effective by counteracting tumor immune suppression.

Dr. Weinberg's team began by studying tumor-infiltrating T lymphocytes, or TIL, collected from patients with solid tumors. "We reasoned that TIL would be a good starting point to identify ongoing tumor-specific T-cell responses," said Dr. Weinberg. Their reasoning led to a remarkable discovery: a new subset of human CD8 T cells capable of recognizing and killing tumors.

"Our studies revealed a novel population of CD8 T cells that is highly enriched for tumor-reactivity in patients with solid tumors," said Dr. Weinberg. "This discovery represents a significant advance in the ability to identify human tumor antigen-specific CD8 T cells among a diverse population of TIL."

The novelty of their discovery lies in the cells' unique characteristics: CD39 and CD103, two immune activation markers, were present on the cells' surfaces, and the cells bear a gene expression signature which appears to keep them confined within the tumor microenvironment. These characteristics, among others, indicate the cells experience chronic stimulation. While they were capable of tumor antigen recognition, it seems their ability to halt cancer progression was impaired.

Undeterred, Dr. Weinberg's team dug deeper, looking for answers in the laboratory. By analyzing expanded T-cell subsets and a tumor cell line from the same patient, they compared the tumor-killing potency of the newly discovered cells to other T cells. In the lab, they demonstrated that only T cells endowed with the CD39\CD103 phenotype killed cancer cells. "Based on these findings, focusing on this novel T-cell population may be a promising approach to boost immune-mediated tumor regression in patients with cancer," said Dr. Weinberg.

ANTI-OX40 THERAPY

Examining the same T-cell population, Dr. Weinberg's team found that patients treated with anti-OX40 showed higher frequencies of T cells bearing the CD39\CD103 phenotype than patients who received conventional therapies. They hypothesized that patients whose TIL contain higher frequencies of these cells will experience greater overall survival.

> We envision this work will provide a partial road map for clinicians to treat cancer patients with immunotherapy for the next 10 to 20 years.

To test this premise, Dr. Weinberg's laboratory is collaborating with R. Bryan Bell, M.D., D.D.S., FACS, and Rom S. Leidner, M.D., assistant members and co-directors, Providence Head and Neck Cancer Program, in a first-in-human clinical trial administering anti-OX40 to patients with head and neck cancer prior to surgery. By comparing patients' tumor and blood samples before and after surgery, they seek to determine whether changes to these T cells following anti-OX40 therapy are associated with improved survival.

"Our hope is that these studies will increase our understanding of how current immunotherapies affect tumor-reactive T cells at the cellular and molecular levels, and to guide the development of new therapies for patients that fail current treatments," said Dr. Weinberg. "We envision this work will provide a partial road map for clinicians to treat cancer patients with immunotherapy for the next 10 to 20 years."

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Hong-Ming Hu, Ph.D., associate member, Cancer Immunobiology Laboratory

Cancer Immunobiology Laboratory

Hong-Ming Hu, Ph.D., is studying the role of autophagy – and antigen cross-presentation in particular – in therapeutic vaccines for patients with cancer.

Autophagy, the process by which cells recycle dysfunctional components and eliminate intracellular pathogens, is a long-standing focus of Dr. Hu's research. From the outset, his laboratory has investigated the role of autophagy in cancer immunotherapy.

Therapeutic cancer vaccines have emerged as a viable immunotherapy strategy. Like other vaccines, cancer vaccines prompt an immediate immune response via the innate immune system, while also stimulating an adaptive immune response and long-term memory to prevent cancer recurrence.

One approach to the development of cancer vaccines is to extract proteins from tumor cells, and prime the immune system to recognize the tumor proteins as foreign. Tumor proteins, also known as tumor antigens, can serve as targets of an effective immune response. However, appropriate antigen selection is essential to activating an effective immune response by vaccination. Similarly, the selection of vaccine adjuvants, a substance that enhances the body's immune response to an antigen, is critical to eliciting cancer immunity.

NANOPARTICLES AS VACCINE ADJUVANTS

Seeking to develop more effective cancer vaccines, Dr. Hu is evaluating the use of nanoparticles as vaccine

adjuvants, and the function of nanoparticles in antigen cross-presentation. Key to inducing cancer immunity by vaccination, antigen cross-presentation entails the ability of certain antigen-presenting cells to acquire, process and present tumor antigens to CD8 T cells, converting naïve CD8 T cells into activated cancer-killers.

As reported in Nanoscale Research Letters, Dr. Hu's lab found that positively charged superparamagnetic iron oxide nanoparticles, or SPIO NPs, had a beneficial effect on antigen cross-presentation and CD8 T-cell activation compared to SPIO NPs with different chemistries. "Nanoparticles modified with different chemistries exhibit diverse biological properties and differ in their adjuvant potentials," said Dr. Hu. "This will make us consider the design of effective and safe vaccine adjuvants more carefully in the future."

UBIQUITIN ENRICHES TUMOR ANTIGENS

While Dr. Hu is testing the ability of nanoparticles to improve the immune responses of T cells, he is also evaluating methods for effective tumor antigen selection and extraction. One strategy is to analyze the role of the ubiquitin pathway in antigen cross-presentation.

Ubiquitin, a small regulatory protein with autophagic functions, modifies other cellular proteins through a process known as ubiquitination, and tags mutated or defective proteins for degradation. When appended to proteins, ubiquitin can also act as an affinity tag, marking the proteins for purification without the need for prior identification of tumor antigens.

His lab examined the function of purified ubiquitinated proteins derived from tumor cells, and their findings, reported in the Journal of Immunotherapy, shed light on the identification of tumor antigens by means of antigen cross-presentation. "Our studies establish that ubiquitinated proteins provide a relevant source of tumor antigens for activating an anti-tumor immune response," said Dr. Hu. "Ubiquitin can be used as an affinity tag to enrich for patients' unique tumor-specific antigens, as well as shared tumor antigens common to many types of cancer," said Dr. Hu.

Our research demonstrates there is potential to develop a shared immune response by vaccination, and these discoveries have application for the next generation of cancer vaccines.

Their discovery may have significant implications for cancer vaccine development, with the potential to invoke immunity against many types of cancer.

CANCER VACCINES 2.0

Research by Dr. Hu's lab has contributed to a better understanding of the functions of nanoparticles and ubiquitinated proteins in antigen cross-presentation, and how they may be used to boost cancer immunity – a partial representation of the advancements made by his lab in illuminating the role of autophagy in cancer immunotherapy.

"When designing cancer vaccines, scientists now realize we need to identify patients' unique tumor-specific antigens, as well as shared antigens, to optimize immune responses," said Dr. Hu. "Our research demonstrates there is potential to develop a shared immune response by vaccination, and these discoveries have application for the next generation of cancer vaccines."

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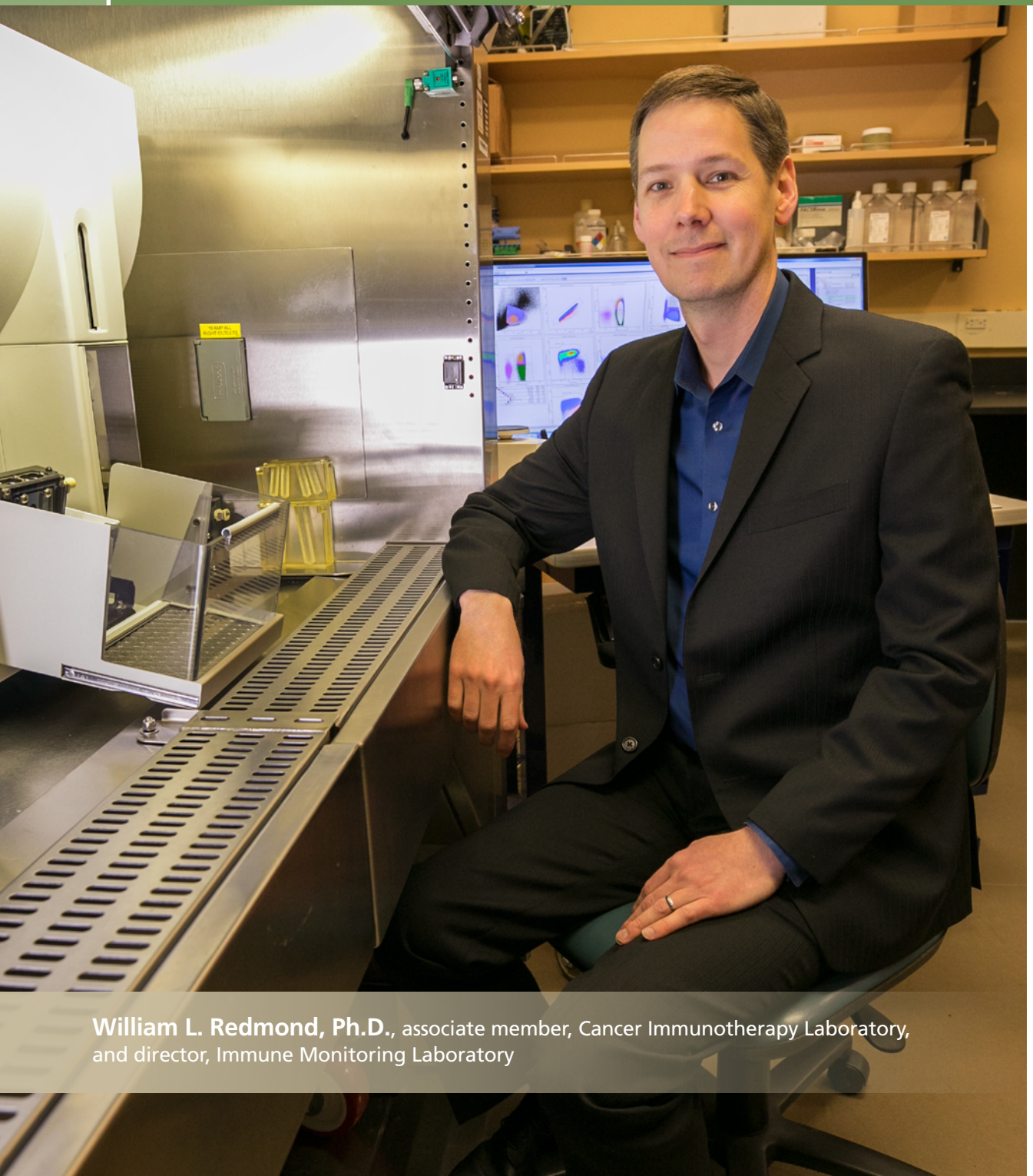

William L. Redmond, Ph.D., associate member, Cancer Immunotherapy Laboratory, and director, Immune Monitoring Laboratory

Cancer Immunotherapy Laboratory

William L. Redmond, Ph.D., is investigating how limiting or reversing tumor-induced immune suppression, together with the administration of immune-modulating antibodies, may improve survival for patients with cancer.

Recent developments in cancer immunotherapy have displayed its potential to improve overall patient survival, particularly when therapies are combined and optimized for maximum clinical benefit. Indeed, for certain cancers, such as melanoma, lung cancer, advanced head and neck cancer and some blood cancers, immunotherapy is now regarded as a standard of care alongside chemotherapy, radiation and surgery.

Yet, as reported in the European Journal of Cancer, Dr. Redmond and colleagues describe several challenges – from treatment dose, schedule and duration to the need for clinical biomarkers – facing the field today. "Even when immunotherapy agents are combined, we find that some patients with cancer do not experience clinical benefit, due in part to the immune-suppressing effects of the tumor microenvironment," said Dr. Redmond. "The next generation of cancer immunotherapy will need to incorporate agents that block or reverse immune suppression to improve overall patient survival."

Dr. Redmond's lab is examining whether inhibition of galectin-3, a protein known to promote cancer growth and immune suppression, enhances the therapeutic effects of immunotherapy.

GALECTIN-3 INHIBITION

Found in a variety of cancer cells, galectin-3 is associated with poor prognosis and is present at high production levels in patients with metastatic cancer. Galectin-3 is also known to attract myeloid-derived suppressor cells, or MDSCs, a type of immune cell with regulatory and suppressive functions. Tumors bearing high infiltration of MDSCs have shown resistance to immunotherapy.

> The next generation of cancer immunotherapy will need to incorporate agents that block or reverse immune suppression to improve overall patient survival.

Dr. Redmond's team speculated that GR-MD-02, a galectin-3 inhibitor, and anti-OX40, an immune-stimulating antibody, would synergize to mediate cancer regression. Using a preclinical model, they studied the combination in cancers of the prostate, breast and connective tissues. Compared to anti-OX40 therapy alone, they observed the therapeutic combination was more effective in reducing the frequency of MDSCs within the tumor microenvironment, thus limiting immune suppression and enhancing overall survival.

In other preclinical studies, they evaluated GR-MD-02 with an anti-PD-1 antibody, a checkpoint immunotherapy approved for several cancers, and found additional evidence of clinical benefit. "Our studies revealed that galectin-3 inhibition in conjunction with immune-modulating antibodies enhanced tumor-specific immunity and improved survival in preclinical models," said Dr. Redmond. "Our next step was to test these novel combinations in patients."

FIRST-IN-HUMAN CLINICAL TRIAL

In collaboration with Brendan D. Curti, M.D., member and director, Cytokine and Adoptive Immunotherapy Program, Dr. Redmond opened a first-in-human, phase I clinical trial testing the safety and immunological effects of GR-MD-02 in combination with pembrolizumab, an anti-PD-1 antibody, in patients with melanoma, lung cancer and head and neck cancer. The investigator-initiated study is a collaboration of Providence Health & Services and the pharmaceutical sponsor with support from the National Cancer Institute.

Of the nine patients enrolled to the trial, five experienced regression of their cancers in response to therapy. "The clinical responses seen in this study are encouraging, and we are making progress on identifying immunological biomarkers that may predict clinical responses," said Dr. Redmond. "As our studies demonstrate, patients who respond to the combination of GR-MD-02 and pembrolizumab may have reduced MDSCs following treatment – a potential biomarker which may guide the development of future studies."

Preliminary results from the clinical trial, along with data from the corresponding preclinical studies, were presented by Dr. Redmond's laboratory at the 2017 annual meeting of the Society for Immunotherapy of Cancer, which awarded the team a Young Investigator Travel Award based on the quality of their research and potential to advance the field.

Drs. Redmond and Curti plan to open another phase I clinical trial in the future, testing GR-MD-02 and an anti-OX40 antibody in patients with metastatic cancer, to offer more patients hope for improved survival.

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Marka R. Crittenden, M.D., Ph.D., associate member, Integrated Therapies Laboratory, and director, Translational Radiation Research, and **Michael J. Gough, Ph.D.**, associate member, Integrated Therapies Laboratory

Integrated Therapies Laboratory

As principal investigators of two R01 Research Project grants from the National Cancer Institute, **Michael J. Gough, Ph.D.**, and **Marka R. Crittenden, M.D., Ph.D.**, are examining the combination of highly targeted radiation therapy with novel immunotherapies for cancer. Together, they lead the Integrated Therapies Laboratory.

The role of radiation therapy as an immunotherapeutic agent is a subject of ongoing research. Yet preclinical studies indicate high-dose radiation therapy is effective in mediating cancer regression when paired with immunotherapy.

In the prevailing theory, radiation therapy eradicates cancer cells, which are processed by the immune system, prompting an influx of cancer-killing CD8 T cells to the tumor site. Checkpoint immunotherapies counteract the immune-suppressing forces of the tumor microenvironment, which enables the elimination of residual cancer cells that survive radiation. Drs. Gough and Crittenden tested this concept, and their findings may guide the combination of these therapies for treating patients with cancer.

RADIATION VS LISTERIA VACCINATION

The bacteria *Listeria* monocytogenes is in development as a potential immune-based cancer therapy. One strategy shown to generate anti-cancer immune responses uses a modified form of *Listeria* as a cancer vaccine.

In a preclinical pancreatic cancer model, Drs. Gough and Crittenden compared high-dose radiation therapy and a *Listeria* vaccine platform. They analyzed the ability of both agents to generate anti-cancer immune responses when combined with an anti-PD-1 antibody, a type of checkpoint immunotherapy. They observed *Listeria* vaccination prompted a greater increase in the number of tumor-reactive T cells than radiation. However, the vaccine failed to provide an advantage over radiation in controlling tumor growth.

"In our experiments, generating large numbers of tumor-reactive T cells by *Listeria* vaccination did not substitute for the efficacy of radiation and an anti-PD-1 antibody," said Dr. Gough. "This leads us to question whether the main driver of radiotherapeutic efficacy is to increase the number of CD8 T cells, and provides guidance for future investigations."

These findings, which confirm the benefits of radiation therapy as a partner for checkpoint immunotherapy, were presented by their lab at the 2017 annual meeting of the Society for Immunotherapy of Cancer.

INNATE AND ADAPTIVE IMMUNITY

In other experiments, Drs. Gough and Crittenden are using *Listeria* vaccination to study innate and adaptive immune responses to cancer. Whereas the innate immune system initiates immune responses, an adaptive immune response can provide long-term immunity.

In a preclinical model, their lab evaluated an approach to amplify the inflammatory immune response to *Listeria* by modifying expression of suppressor of cytokine signaling 1, or SOCS1, a protein known to suppress inflammation. They reasoned loss of the SOCS1 protein in dendritic cells, a cell that links innate and adaptive immune responses, would boost immune activation and increase T-cell responses.

> We demonstrated for the first time that cell-specific loss of SOCS1 in dendritic cells in vivo redirects the immune response following *Listeria* vaccination away from an adaptive response and toward an innate response.

By testing the *Listeria* vaccine in dendritic cells engineered to lack SOCS1, they compared results from in vitro experiments with those performed in living organisms, known as in vivo experiments. Contrary to their expectations, they observed a decrease in CD8 T-cell responses. As reported in the Journal of Immunology, dendritic cells lacking SOCS1 expression were functional, but failed to generate an efficient adaptive immune response. When the innate immune response increased, the adaptive immune response decreased.

"We demonstrated for the first time that cell-specific loss of SOCS1 in dendritic cells in vivo redirects the immune response following *Listeria* vaccination away from an adaptive response and toward an innate response," said Dr. Crittenden. "Strategies that aim to generate cancer immunity by means of CD8 T-cell meditation may need to avoid over-activation of cross-presenting dendritic cells to optimize the adaptive immune response."

Their discovery, albeit surprising, is yielding new directions of research. Drs. Gough and Crittenden have applied these insights to other areas of investigation in their laboratory with the hope of improving therapies for patients with cancer.

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Pryke KM et al: A novel agonist of the TRIF pathway induces a cellular state refractory to replication of Zika, Chikungunya, and Dengue viruses. MBio. 2017; 8(3):e00452-17. PMID: 28465426.

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Eight of nine publications shown.

Bernard A. Fox, Ph.D., member and Harder Family Endowed Chair for Cancer Research, Molecular and Tumor Immunology Laboratory

Molecular and Tumor Immunology Laboratory

An expert in tumor immunology and immune profiling, **Bernard A. Fox, Ph.D.**, is investigating immunotherapy mechanisms of action and methods of tumor immune escape. By developing novel biomarkers, his lab is advancing technology which may help clinicians predict patient responses to therapy.

The development of checkpoint immunotherapies improved clinical outcomes for patients with melanoma, lung cancer and other malignancies. Yet for patients with breast cancer, the second-leading cancer diagnosis among women in the United States, these therapies provided limited benefit.

Seeking to optimize clinical benefit for these patients, Dr. Fox and his team examined whether the timing and sequence of immunotherapy combinations affect clinical outcomes. Their findings reveal significant insights, which may improve the administration of cancer care and immunotherapy clinical trials for patients with breast cancer and other malignancies.

IMMUNOTHERAPY SEQUENCING

In a preclinical breast cancer model, his lab tested the combination of two immune-modulating antibodies – anti-PD-1 and anti-OX40 – compared to both therapies given alone, which yielded unexpected findings. “We were really surprised to see the simultaneous combination of anti-OX40 and anti-PD-1 was less effective than either therapy given alone,” said Dr. Fox. Equally surprising, when anti-OX40 was given prior to anti-PD-1, but not

in the reverse order, the sequential combination showed the greatest clinical benefit of all their study models.

"The timing and sequence of the two agents had a profound impact on their biological effects," said Dr. Fox. Anti-OX40 administered prior to anti-PD-1 provided an apparent 30 percent cure rate in a previously incurable model. These results, published in Clinical Cancer Research, drew the attention of the National Cancer Institute and the American Association for Cancer Research. In articles featuring Dr. Fox's study, both organizations noted the need for a better understanding of the biological mechanisms of action when immunotherapies are combined in clinical trials.

> By examining tissue biomarkers in an individual patient's tumor, doctors may be able to make better predictions of which immunotherapies will generate the most effective anti-cancer immune response.

"Our research demonstrates the need for well-controlled clinical trials of immunotherapy combinations. I think that is how we are going to make greater progress against cancer," said Dr. Fox.

IMMUNE PROFILING

To evade detection and elimination by the immune system, tumors employ multiple mechanisms of immune escape. By analyzing patients' immune profiles and their tumors, such as the type and frequency of tumor-killing T cells that infiltrate tumors and how tumors escape detection, clinicians may gain valuable insights to guide their treatment strategies.

As an investigator of the global Immunoscore study, an independent prognostic tool shown to predict recurrence and survival in patients with colorectal cancer, Dr. Fox and his lab are at the forefront of developing prognostic biomarkers for cancer. In collaboration with his Immunoscore co-investigator Carlo B. Bifulco, M.D., member and director, Translational Molecular Pathology, along with R. Bryan Bell, M.D., D.D.S., FACS, and Rom S. Leidner, M.D., assistant members and co-directors, Providence Head and Neck Cancer Program, Dr. Fox assessed the immune profiles of 119 patients with HPV-negative oral squamous cell carcinoma, a type of head and neck cancer.

Using multispectral imaging and objective assessment tools, they performed the first comprehensive immune profiling study of patients with this disease. Evaluation of six biomarkers revealed a positive correlation between patient survival and increased tumor-infiltrating T cells, with a concurrent absence of immune suppression mechanisms.

"By examining tissue biomarkers in an individual patient's tumor, doctors may be able to make better predictions of which immunotherapies will generate the most effective anti-cancer immune response," said Dr. Fox. "Our study suggests that the evaluation of multiple parameters is necessary to identify patients in need of more aggressive treatment strategies."

Dr. Fox presented results of the study at a joint workshop of the Food and Drug Administration and the American Association for Cancer Research. His lab is collaborating with colleagues around the world to improve technologies and assessment techniques needed for the development of validated biomarkers to aid clinicians in real-time decision-making.

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Seven of 12 publications shown.

Kristina H. Young, M.D., Ph.D., assistant member,
Tumor Microenvironment Laboratory

Tumor Microenvironment Laboratory

As a radiation oncologist and immunologist, **Kristina H. Young, M.D., Ph.D.,** is studying how immunotherapy can remodel patients' tumor environments to increase the effectiveness of conventional cancer therapies.

For patients with colorectal cancer, the most common cancer among men and women in the United States after breast, prostate and lung cancers, conventional cancer therapies – chemotherapy, radiation and surgery – have been the mainstay of treatment for decades. Nevertheless, colorectal cancer remains the fourth-leading cause of cancer death in this population, prompting a surge of investigation into combining immunotherapy and conventional therapy to improve survival. Dr. Young leads an innovative clinical trial testing a novel immunotherapy in combination with chemoradiation, offering hope to patients with this lethal disease.

TUMOR IMMUNE INFILTRATION

Studies show a correlation between patient survival and infiltration of their tumors by cancer-killing CD8 T cells, regulatory T cells, known as Tregs, and macrophages, another immune cell with regulatory functions. Tumors exhibiting little infiltration of CD8 T cells, increased macrophage infiltration and a high ratio of Tregs to CD8 T cells are associated with a poor tumor immune profile, or low immune score. In patients with colorectal cancer, low immune scores are linked to decreased overall survival, and high scores correlate with improved survival.

Seeking to improve prognosis for these patients, Dr. Young studied whether modifying patients' tumor immune environments can improve their responses to therapy. She tested whether inhibiting transforming growth factor beta, or TGF-ß – a protein with important immune signaling functions, would increase the effectiveness of radiation therapy.

TGF-ß INHIBITION

Through its signaling pathway, TGF-ß aids in cellular proliferation and differentiation, and the activation of immune cells. In cancer cells, however, mutations may alter the signaling pathway, leading to cancer growth and a tumor environment with poor immune infiltration. Blocking the TGF-ß pathway can disrupt these cancer-promoting forces.

"Our experiments demonstrate that pretreatment TGF-ß blockade improved the tumor immune environment in preclinical models, and significantly improved the effectiveness of subsequent radiation therapy," said Dr. Young. "We demonstrated that this effect was entirely dependent on CD8 T cells, and generated long-term, tumor-specific protection."

ONE-OF-A-KIND CLINICAL TRIAL

Armed with promising preclinical data, Dr. Young wasted no time in offering this novel combination to patients with colorectal cancer. By participation in her phase II, investigator-initiated study – the first of its kind worldwide, patients diagnosed with stage II and higher rectal cancer who are slated for conventional therapy may opt to receive immunotherapy as part of their treatment regimens.

Galunisertib, a small molecule inhibitor of TGF-ß, is administered to patients in the form of daily pills for two weeks prior to radiation and chemotherapy, and continued throughout their treatments.

Of 50 patients expected to participate, the first three patients experienced a dramatic response: one patient's tumor disappeared completely, and the others had more than a 75 percent decrease in tumor size, with equally impressive responses in their lymph nodes.

> Our studies demonstrate there are significant opportunities to manipulate the immune environment of tumors for therapeutic gain.

The study also seeks to evaluate patients' immune scores as potential biomarkers to predict therapeutic response. By monitoring patients' immune responses throughout treatment, and correlating changes in their tumor immune infiltrate to imaging analysis and treatment response, Dr. Young hopes to aid in the development of a prognostic tool to guide treatment decisions. In patients who respond to treatment, she expects to see remodeling of their tumor environments toward a more favorable immune score with increased CD8 T cells, decreased macrophages and a low Treg:CD8 T-cell ratio.

"Our studies demonstrate there are significant opportunities to manipulate the immune environment of tumors for therapeutic gain. These initial responses are very exciting and make us hopeful that this therapy will improve outcomes for patients with this deadly disease," said Dr. Young.

Preliminary results were presented by her lab at the 2017 annual meetings of the American Society for Radiation Oncology and the Society for Immunotherapy of Cancer, among other conferences.

PUBLICATIONS:

Baird JR, Feng Z, Xiao HD, Friedman D, Cottam B, Fox BA, Kramer G, Leidner RS, Bell RB, Young KH, Crittenden MR, Gough MJ: STING expression and response to treatment with STING ligands in premalignant and malignant disease. PLoS One. 2017; 12(11):e0187532. PMID: 29135982.

David B. Page, M.D., assistant member, Breast Cancer Immunotherapy, and **Alison K. Conlin, M.D., MPH,** associate member and medical director, Providence Breast Cancer Medical Program and High-Risk Breast Clinic

Breast Cancer

Together, **Alison K. Conlin, M.D., MPH,** and **David B. Page, M.D.,** oversee a vast portfolio of clinical trials and therapies for patients with breast cancer. From early-stage disease to metastatic and triple-negative breast cancer, they seek to improve quality of life and survival for patients with this pervasive cancer.

In addition to being the most common cancer among women in the United States after skin cancer, breast cancer is also one of the deadliest, second only to deaths from lung cancer. By conducting novel studies, Drs. Conlin and Page hope to improve breast cancer care so that more patients will benefit.

PREOPERATIVE IRX-2

Dr. Page devised a phase I clinical trial testing an experimental immunotherapy in women and men diagnosed with stage I-III breast cancer. The study includes patients with triple-negative breast cancer, a type of breast cancer in which three common receptors – estrogen, progesterone and HER2 – are absent, making it one of the most difficult forms to treat. He examined whether IRX-2, an immune-boosting cytokine therapy shown to shrink tumors in other cancers, improves clinical responses when administered prior to surgery.

For 10 consecutive days, patients received local injections of IRX-2 as preoperative therapy. A mild chemotherapy was also administered prior to surgery to deplete T regulatory cells, a type of immune-suppressing cell. Tumor and blood samples were assessed for the

presence of immune activation markers and tumor-infiltrating lymphocytes, or TILs – signs that IRX-2 treatment boosted patients' immune responses. TILs are associated with improved survival in patients with early-stage breast cancer.

"We found that IRX-2 was well-tolerated with preliminary evidence of increased TIL recruitment, peripheral lymphocyte activation and T-regulatory depletion," said Dr. Page. He presented early results of the trial, which is ongoing, at the 2017 annual meeting of the Society for Immunotherapy of Cancer.

HER2CLIMB

Roughly 20 percent of breast cancers test positive for HER2, a protein known to promote cancer growth. HER2-positive tumors can spread more quickly and are less sensitive to hormone therapy than other types of breast cancer.

> These women, many whose cancers had spread to the brain, benefited from extended disease survival for a significant period of time.

Therapies that target the HER2 protein can be effective, particularly in early-stage disease. For patients with metastatic cancer, however, five-year survival outcomes are a dismal 22 percent. "When treating metastatic breast cancer, often our goal is to halt its growth and keep it from traveling to new places in the body," said Dr. Conlin. Brain metastases are common in patients with advanced disease.

An investigator on the global HER2CLIMB study, Dr. Conlin is evaluating whether tucatinib, an experimental inhibitor of HER2, might improve survival in patients with HER2-positive breast cancer. The phase I/II study tests tucatinib in combination with targeted therapies in patients with locally advanced or metastatic HER2-positive breast cancer.

The study is ongoing, and preliminary results were presented at the European Society for Medical Oncology 2017 Congress and the 2017 San Antonio Breast Cancer Symposium. "Our findings demonstrate 20 percent of patients treated with tucatinib combinations for advanced breast cancer were free of progressing disease at 16 months or more," said Dr. Conlin. "These women, many whose cancers had spread to the brain, benefited from extended disease survival for a significant period of time."

CANCER-RELATED FATIGUE

Designated a high-priority area of research by the National Cancer Institute, cancer-related fatigue, or CRF, is a common complaint among breast cancer patients, affecting quality of life and treatment adherence. Dr. Conlin engaged in a nationwide, longitudinal study comparing CRF in women with breast cancer to women without cancer. "We found that breast cancer survivors experience significantly more CRF prior to and after chemotherapy compared to healthy patients," said Dr. Conlin.

Study results drew the attention of the American Society of Clinical Oncology, which published the findings and an accompanying editorial in its Journal of Clinical Oncology. The society, whose annual report noted CRF management among the most important patient care advances of the year, also selected the study for presentation at its 2017 annual meeting.

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Brendan D. Curti, M.D., member and director, Cytokine and Adoptive Immunotherapy Program, Genitourinary Oncology Research and Providence Melanoma Program

Cytokine and Adoptive Immunotherapy

An expert in cytokine and adoptive immunotherapy, **Brendan D. Curti, M.D.,** is engaged in numerous investigator-initiated and industry-sponsored clinical trials to improve survival of patients with cancer.

Cytokines are proteins with cell-signaling functions important in regulating immune responses, and are instrumental in rejecting cancers. Interleukin-2, known as IL-2, is a type of immune-boosting cytokine proven to be effective when administered in high doses to patients with melanoma and renal cell carcinoma, a type of kidney cancer. Dr. Curti oversees one of the busiest programs in the country for high-dose IL-2, and the largest program on the West Coast.

PROCLAIM STUDY

Like other immunotherapies, IL-2 can induce unexpected complications, such as immune-related adverse events – or irAEs, ranging from reversible symptoms to potentially life-threatening side effects. Common irAEs include thyroid dysfunction and vitiligo, a condition causing the loss of skin color. While some studies suggest a positive association between irAEs and patient survival, consensus among medical professionals is lacking.

Seeking to provide contemporary assessment of the relationship between clinical benefit and irAEs from IL-2, Dr. Curti is the lead author of a nationwide, multicenter observational study, known as PROCLAIM,

to evaluate the treatment patterns and clinical responses of high-dose IL-2 in patients with metastatic renal cell carcinoma and metastatic melanoma. Of the 1,535 patients enrolled to the study from 2008 to 2016, 130 patients experienced irAEs. As reported in the Journal for ImmunoTherapy of Cancer, the development of irAEs related to IL-2 is associated with significantly improved overall survival compared to patients with no irAEs.

"Our study supports the association of immune activation from immunotherapy with better patient outcome," said Dr. Curti. "Although it would be ideal for patients to have immunotherapy with no side effects, this work supports that clinical benefit is linked with side effects related to the immune activity of IL-2."

PIVOT-02 STUDY

Dr. Curti is investigating another cytokine showing promise when given with checkpoint immunotherapy in patients with advanced solid cancers. As a lead investigator of the phase I/II multicenter clinical trial known as PIVOT-02, he is studying NKTR-214, a chemically modified form of IL-2, given in combination with nivolumab, an anti-PD-1 checkpoint immunotherapy approved for treating a variety of cancers.

Preclinical studies indicate NKTR-214 boosts the proliferation of cancer-killing CD8 T cells within the tumor microenvironment without increasing the activity of immune-suppressing T regulatory cells. These properties are due to its pegylation, a chemical modification which alters the receptor binding of IL-2. NKTR-214 also enhances expression of PD-1, an immune checkpoint protein responsible for regulating immune responses. Through inhibiting PD-1, nivolumab increases the life span and activity of T cells, which can facilitate the destruction of cancer. Investigators hypothesized that the complementary mechanisms of action of these two immunotherapies would result in greater overall survival than seen in either therapy alone.

When given as first- or second-line therapy to 38 patients with multiple tumor types, responses were observed in 46 percent of patients with renal cell carcinoma, 64 percent with melanoma, and 75 percent with non-small cell lung cancer. Patients with bladder cancer and triple-negative breast cancer are also eligible to enroll.

> Our study supports the association of immune activation from immunotherapy with better patient outcome.

"By increasing the proliferation of CD8 T cells in the tumor and increasing PD-1 expression, NKTR-214 demonstrated a potentially synergistic mechanism with anti-PD-1 therapy, confirming observations from the preclinical studies," said Dr. Curti. "These data demonstrate that NKTR-214 and nivolumab are well-tolerated in the outpatient setting with encouraging response rates, and warrant further investigation."

Investigators aim to enroll 350 patients across 13 cohorts in the phase II study, and a second study arm was added to test NKTR-214 in combination with nivolumab and ipilimumab, another checkpoint immunotherapy approved for several cancers. The study was selected for oral abstract presentation at the 2017 annual meeting of the Society for Immunotherapy of Cancer, and presented at other major conferences in the United States and Europe.

PUBLICATIONS:

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Pippa H. Newell, M.D., assistant member and medical director, Providence Liver Cancer Clinic, and **Todd S. Crocenzi, M.D.,** associate member and director, Gastrointestinal Oncology Research

Gastrointestinal Cancer

From novel surgical techniques to innovative immunotherapy studies, **Todd S. Crocenzi, M.D.**, and **Pippa H. Newell, M.D.**, seek to improve outcomes for patients with gastrointestinal cancers.

MISMATCH-REPAIR BREAKTHROUGH

In collaboration with researchers at Johns Hopkins University, Dr. Crocenzi demonstrated that patients with advanced colorectal cancer were responsive to anti-PD-1 checkpoint immunotherapy when their tumors were defective in repairing mismatched DNA.

This deficiency, known as mismatch repair – or MMR, occurs when cells lack the ability to correct errors in DNA replication. When left uncorrected, these errors – known as mutations – accumulate in vast quantities, acting as targets of anti-tumor immune responses. A phase II study by Dr. Crocenzi and colleagues revealed that pembrolizumab, an anti-PD-1 checkpoint inhibitor approved for numerous cancers, was effective in mediating cancer regression in patients with MMR-deficient colorectal cancers bearing high numbers of mutations.

While only a minority of patients with colorectal cancer have MMR-deficient tumors, the investigators hypothesized that other patients who shared the deficiency would also benefit from anti-PD-1 therapy regardless of where their tumors originated. They tested this premise by expanding their study to include 12 types of advanced MMR-deficient cancer, such as pancreas, prostate, uterine and bone cancers.

As reported in the journal Science, their premise was correct: 66 of 86 patients enrolled to the trial saw their tumors shrink or stabilize. In 18 of those responders, their tumors vanished completely. "Based on these responses, our estimates of overall survival at one and two years were 76 percent and 64 percent, which is markedly higher than expected due to the advanced state of disease in these patients," said Dr. Crocenzi.

The results drew national headlines, including an article in The New York Times, and spurred the Food and Drug Administration to accelerate approval of pembrolizumab for MMR-deficient cancers, marking the first instance of a cancer drug approval based on a shared genetic profile rather than cancer type or site of origination.

> These results tie immunity, cancer genetics and therapeutics together in a manner that will likely establish a new standard of care.

Testing for MMR deficiency is widely available, and the investigators estimate up to 60,000 cancer patients annually could benefit. "These results tie immunity, cancer genetics and therapeutics together in a manner that will likely establish a new standard of care," said Dr. Crocenzi.

HCC APPROVAL

For patients with advanced hepatocellular carcinoma, or HCC – the most common type of primary liver cancer, outcomes remain poor, limited by a lack of treatment options. Dr. Crocenzi and other collaborators conducted a phase I/II study of nivolumab, another anti-PD-1 checkpoint inhibitor, in patients with HCC.

In an article for The Lancet, they reported a favorable safety profile and early evidence of clinical activity. Dr. Crocenzi presented preliminary results of the study at the 2017 annual meeting of the American Society of Clinical Oncology, where he noted durable responses were observed with long-term survival. Soon after, the FDA granted nivolumab accelerated approval for patients with advanced HCC whose cancers progressed following systemic therapy – the first immunotherapy approved for this population.

FRS VALIDATION

As a liver and pancreas surgeon, Dr. Newell is engaged in studies to improve surgical techniques and patient outcomes. With colleagues at Providence Cancer Institute, she evaluated a risk assessment tool to predict the postsurgical onset of pancreatic fistula following pancreaticoduodenectomy – the most common operation to treat pancreatic cancer – also known as a Whipple procedure. Consisting of abnormal communication between the pancreas and surrounding organs, pancreatic fistula is the most common complication arising from this procedure, and can be life-threatening.

They conducted a prospective assessment of four centers in the United States and Canada, evaluating the use of Fistula Risk Score, or FRS, in a total of 444 patients undergoing the operation. As reported in the journal HPB, their findings strengthened the clinical validity of FRS. "We can now predict the risk of pancreatic fistula intraoperatively with satisfactory accuracy," said Dr. Newell.

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Carlo B. Bifulco, M.D., member and director, Translational Molecular Pathology, and medical director, Molecular Genomics

Genomics

An expert in translational molecular pathology, **Carlo B. Bifulco, M.D.,** is engaged in numerous studies to characterize the tumor immune environment through genome sequencing and advanced immunohistochemistry and image analysis techniques.

PERSONALIZED MEDICINE

In the past decade, advances in genome sequencing have enabled real-time, high-throughput DNA sequencing – also known as next-generation sequencing, or NGS. As the costs of NGS continue to fall, access by physicians and patients to this powerful diagnostic and predictive tool has increased, and ushered in a new era of personalized medicine.

As medical director of Molecular Genomics, Dr. Bifulco leads the Oregon hub of Providence Personalized Medicine Program, the systemwide NGS program of Providence St. Joseph Health. The program is available to test samples from patients with solid tumors and blood cancers who are receiving standard-of-care therapies or participating in clinical trials. Tests include targeted panels, whole exome and RNA sequencing.

Dr. Bifulco is aided by computational and systems biologist Brady Bernard, Ph.D., genomic scientist Brian Piening, Ph.D., and a team of bioinformaticists. They use state-of-the-art equipment, custom-built bioinformatics pipelines and sophisticated computational models to identify genetic mutations in patients' tumors. Some mutations may be targeted therapeutically, lending valuable insight to clinicians for the development of individualized treatment plans based on patients' unique genetic profiles.

PRECISION IMMUNOTHERAPY

Through the integration of genomics and immunotherapy, it is now possible to identify neoantigens, proteins encoded by tumor-specific mutated genes, to serve as targets of immunotherapy.

> We hope the knowledge acquired through genome sequencing will lead us to cures for cancer.

With extensive experience in the development of NGS assays for immune profiling, Dr. Bifulco's team is at the forefront of harnessing the power of genomics for precision immunotherapy. "We developed a comprehensive solid tumor NGS panel with the dual purpose of detecting clinically relevant, targetable regions of the genome and identifying neoantigens for immunotherapy applications," said Dr. Bifulco.

They were invited to give presentations highlighting their expertise in NGS for immunotherapy at the 2017 annual meeting of the Association for Molecular Pathology.

TRI-SEQ NGS STUDY

In collaboration with Rom S. Leidner, M.D., assistant member and co-director, Providence Head and Neck Cancer Program, and other investigators, Dr. Bifulco leads a clinical trial to study the effects of patients' genomes on their responses to immunotherapy. The study, known as Tri-Seq NGS, aims to characterize neoantigens by harnessing three complementary levels of genetic data: tandem DNA and RNA sequencing from tumor samples, and DNA sequencing from normal tissue. Dr. Bifulco's team uses novel computational approaches to mine for molecular differences between tumor and normal cells that can be targeted by immunotherapies.

The study supports essential functions of the Antitumor T-cell Response Laboratory led by Assistant Member Eric Tran, Ph.D. Dr. Tran is an expert in adoptive cell therapy, a promising approach to curing cancer by amplifying patients' tumor-killing T cells in the lab and giving them back to patients in greater quantities. Dr. Tran will partner with Dr. Bifulco and other clinicians to create highly personalized, genome-guided immunotherapies.

Tri-Seq NGS is open to patients with head, neck, pancreas and other types of cancer, and Dr. Tran plans to begin clinical trials as early as 2019. "We hope the knowledge acquired through genome sequencing will lead us to cures for cancer," said Dr. Bifulco.

IMMUNOSCORE

Together with Bernard A. Fox, Ph.D., member and Harder Family Chair, Molecular and Tumor Immunology Laboratory, Dr. Bifulco serves on a global study supported by the Society for Immunotherapy of Cancer to incorporate the immune contexture into cancer staging and classification. By analyzing the immune contextures of more than 3,000 cancer patients, investigators have developed a new scoring system, known as Immunoscore, to help predict patient outcomes to therapy.

An article in the Journal of Translational Medicine co-written by Dr. Bifulco suggests Immunoscore may become a new component of cancer classification based on immune parameters. "This will represent the first standardized immune-based assay for classifying cancer in the era of immunotherapy," said Dr. Bifulco.

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Rom S. Leidner, M.D., assistant member and co-director, Providence Head and Neck Cancer Program, and **R. Bryan Bell, M.D., D.D.S., FACS,** assistant member and medical director, Providence Head and Neck Cancer Program and Clinic

Head and Neck Cancer

As co-directors of Providence Head and Neck Cancer Program, **Rom S. Leidner, M.D.**, and **R. Bryan Bell, M.D., D.D.S., FACS**, oversee one of the largest immunotherapy clinical trial portfolios for head and neck cancer on the West Coast.

Head and neck cancer accounts for nearly 50,000 new cancer diagnoses in the United States annually, and is the sixth most common cancer worldwide. While five-year survival rates for early-stage disease are 83 percent, only 38 percent of patients with advanced cancers survive beyond five years. Drs. Bell and Leidner lead innovative immunotherapy studies to improve survival for these patients.

ANTI-OX40 PHASE I STUDY

Head and neck squamous cell carcinomas, or HNSCC, are known to produce suppressive factors which can impair anti-cancer immune responses. Drs. Bell and Leidner hypothesized that anti-OX40, an experimental immune-stimulating antibody developed at the Earle A. Chiles Research Institute, may enhance the activation of tumor-killing T cells when administered before surgery. They are testing this concept in an investigator-initiated, phase I clinical trial to evaluate the effectiveness and safety of anti-OX40 given before conventional surgical resection in patients with locally advanced HNSCC.

Beginning two weeks before surgery, patients received intravenous infusion of anti-OX40. Tumor and blood samples were obtained prior to anti-OX40 treatment and at the time of surgery to assess the effects of anti-OX40

on tumor-infiltrating immune cell populations and other immunological functions. The study is the most in-depth analysis of immune response conducted in a surgical trial, representing a pioneering collaboration with their clinical and scientific colleagues.

Dr. Bell presented preliminary results at the 2017 International Conference on Oral and Maxillofacial Surgery. "We found that preoperative anti-OX40 is feasible and safe in patients with HNSCC, and results in the activation and proliferation of T-cell populations in both the tumor microenvironment and in circulation," said Dr. Bell. Results from the ongoing study were also presented at the 2017 Head and Neck Cancer Conference, a joint meeting of the American Association for Cancer Research and the American Head and Neck Society.

ADOPTIVE CELL THERAPY

Dr. Leidner is the first investigator in Oregon to offer patients with HNSCC adoptive cell therapy, or ACT. Celebrated as the Advance of the Year by the American Society of Clinical Oncology, ACT is a highly personalized immunotherapy in which patients' tumor-killing T cells are extracted, reinforced in a lab and reinfused in greater quantities.

Studies show the clinical benefit of ACT in cancers that bear many genetic mutations, or are virally associated. In collaboration with Brendan D. Curti, M.D., member and director, Cytokine and Adoptive Immunotherapy Program, Dr. Leidner is testing the safety and effectiveness of ACT in HNSCC, a cancer associated with human papillomavirus and a high number of mutations.

In the phase II, multicenter study, patients receive reinfusion of their enhanced tumor-infiltrating lymphocytes, followed by interleukin-2, another immunotherapy shown to boost anti-cancer immune responses. The study is ongoing, and preliminary results were presented at the 2017 annual meeting of the Society for Immunotherapy of Cancer.

LIRILUMAB GLOBAL STUDY

In another phase I/II trial, Dr. Leidner is evaluating a combination of two immunotherapies for patients with advanced HNSCC and other solid tumors.

Natural killer cells, or NK cells, play a critical role in immune surveillance and controlling tumor growth. Activation of NK cells is regulated in part by killer-cell immunoglobulin-like receptors, known as KIRs. Blocking KIR function may facilitate anti-cancer immune responses, and synergize with other immunotherapies. To test this premise, Dr. Leidner is leading the global investigation of lirilumab, an experimental NK-cell inhibitor, in combination with nivolumab, an immune checkpoint inhibitor approved for several cancers.

> We observed encouraging responses that were deep and durable in some patients.

The study was presented at the 2017 International Congress on Targeted Anticancer Therapies, where preliminary results demonstrated clinical benefit. Of 41 patients with HNSCC, 52 percent saw their tumors shrink or stabilize in response to therapy. "We observed encouraging responses that were deep and durable in some patients," said Dr. Leidner. "These findings warrant further study of this novel combination."

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Eight of 11 publications shown.

John E. Godwin, M.D., MS, member and program leader, Hematologic Malignancies

Hematologic Malignancies

John E. Godwin, M.D., MS, is investigating novel immunotherapies for patients with hematologic malignancies, also known as blood cancers.

Acute myeloid leukemia, or AML – a type of cancer arising from abnormal development of blood cells in the bone marrow, is a common type of leukemia in the United States; approximately 19,500 people are newly diagnosed each year. An acute disease that can progress rapidly if untreated, it is the most deadly leukemia among adults, with less than 28 percent of adult AML patients surviving beyond five years.

Also resulting from abnormal bone marrow cells, myelodysplastic syndromes, or MDS, are hematologic conditions marked by low numbers of blood cells. An estimated 14,000 new diagnoses of MDS occur annually, most of them in older adults.

Considered a type of blood cancer, patients with MDS are assessed for their risk of developing AML. The World Health Organization classifies MDS by five risk groups ranging from very low risk to very high risk. For patients in the intermediate risk group, an estimated 33 percent will develop AML within five years; in very high-risk patients, the chance of developing AML within five years jumps to 84 percent.

FIRST-IN-HUMAN STUDY

Dr. Godwin is among a global cohort of investigators testing a new immunotherapy in a phase I, first-in-

human study of adult patients with AML and MDS. Flotetuzumab, a bispecific antibody administered by intravenous infusion, is capable of binding to two distinct cell-surface molecules simultaneously. Through dual recognition of CD123, a molecule overexpressed in hematologic malignancies like AML and MDS, and CD3, another molecule known to stimulate the activity of cancer-killing T cells, flotetuzumab can redirect T cells toward their malignant targets.

> We have seen leukemia patients who are unresponsive to other therapies go into complete remission with this immunotherapy.

While immunotherapy is effective in other cancers such as B-cell hematologic malignancies, AML has remained resistant to antibody-based therapies due to a lack of appropriate molecular targets. Yet for more than 90 percent of patients with AML, CD123 is highly expressed; in patients with MDS, the molecule is prevalent in more than 50 percent of patients. With evidence of anti-leukemic activity in preclinical studies of flotetuzumab, study investigators hoped the bispecific therapy would bring clinical benefit to patients with these formidable malignancies.

The study, which is ongoing, is testing the safety and effectiveness of flotetuzumab in patients with refractory or relapsed AML, or intermediate to high-risk MDS. Of 13 sites participating worldwide, five are in the United States, and Dr. Godwin is the only investigator on the West Coast enrolling patients to the study.

Early results were presented at major conferences across the United States and Europe. At the 2017 annual meeting of the American Society of Hematology, Dr. Godwin was invited to present preliminary data in an oral abstract session. Of 57 patients participating in the trial, a minority were enrolled to a dose expansion cohort to determine the maximum tolerated dose. Among this group, 75 percent demonstrated anti-leukemic activity, and two patients experienced a complete response.

"We have seen leukemia patients who are unresponsive to other therapies go into complete remission with this immunotherapy," said Dr. Godwin. "These early study results are encouraging, and warrant further investigation."

CHECKPOINT COMBINATION

In another abstract selected for presentation by the American Society of Hematology, Dr. Godwin, together with Bernard A. Fox, Ph.D., member and Harder Family Chair, Molecular and Tumor Immunology Laboratory, and Carlo B. Bifulco, M.D., member and director, Translational Molecular Pathology, and other investigators, reported translational results of the flotetuzumab study which support the rationale for its combination with anti-PD-1 checkpoint immunotherapy.

Through advanced multispectral immuno-histochemistry analysis, Dr. Godwin and colleagues assessed malignant and normal tissue samples from patients in the study. They observed synergistic anti-cancer activity in AML treated with flotetuzumab and an anti-PD-1 checkpoint inhibitor. "These data suggest that combination with anti-PD-1 therapy may enhance the therapeutic effects of flotetuzumab in patients with refractory or relapsed AML," said Dr. Godwin.

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Brendan D. Curti, M.D., member and director, Cytokine and Adoptive Immunotherapy Program, Genitourinary Oncology Research and Providence Melanoma Program, and **Walter J. Urba, M.D., Ph.D.,** member, director and endowed chair of Cancer Research

Melanoma

As experts in the clinical development of immunotherapy for melanoma, **Brendan D. Curti, M.D.**, and **Walter J. Urba, M.D., Ph.D.**, investigate combinations of experimental treatments and standard-of-care therapies to improve patient survival.

MITCI STUDY

Dr. Curti leads a phase I, investigator-initiated clinical trial of CVA21, an oncolytic and immunotherapeutic strain of coxsackievirus A21, in combination with standard-of-care ipilimumab, an anti-CTLA-4 immune checkpoint inhibitor, in patients with advanced melanoma.

The study, known as Melanoma Intra-Tumoral Cavatak and Ipilimumab, or MITCI, is a collaboration between Providence Health & Services and the pharmaceutical sponsor. Patients receive injections of CVA21 in their melanoma lesions, followed by intravenous ipilimumab. A total of 60 patients are expected to participate at 10 centers across the country.

A novel, non-genetically modified form of a common cold virus, CVA21 targets a protein called ICAM that is highly expressed on the surfaces of many cancer cells. Once CVA21 attaches to ICAM, it can infect and kill cancer cells. In preclinical studies, the death of cancer cells induced by CVA21 primed the immune system to recognize and destroy malignancies, suggesting a potential synergy when it is combined with checkpoint inhibitors and other immunotherapies.

In recent years, the number of treatments for patients with advanced melanoma has increased with the development of immune checkpoint inhibitors. However, not all patients respond to these therapies, and some patients who respond initially develop disease progression later. "These patients have few treatment options and a poor outlook," said Dr. Curti.

At the 2017 annual meeting of the American Association for Cancer Research, Dr. Curti presented early results, reporting better responses in patients who received the combination compared to patients who received either therapy given alone in prior studies. "A significant number of patients experienced regression of their cancers," said Dr. Curti. "The CVA21-ipilimumab combination may represent a valuable treatment option for an unmet need in patients with advanced melanoma," said Dr. Curti.

CHECKPOINT-INDUCED TUMOR EVOLUTION

In another multicenter phase I study, Dr. Urba and colleagues evaluated the mechanisms by which checkpoint inhibition modulates tumor evolution in patients with advanced melanoma.

As reported in the journal Cell, they observed changes in patients' tumors in response to treatment with nivolumab, an anti-PD-1 checkpoint inhibitor. Through DNA, RNA and T-cell receptor sequencing, they found the tumor mutation burden – the number of mutations within a tumor genome – was reduced in responding tumors. A high tumor mutation burden is associated with an increase in neoantigens – proteins encoded by tumor-specific mutated genes which may serve as targets of checkpoint inhibitors.

They also observed an increase in immune cell infiltration of responding tumors, and the expansion of specific T-cell clones. "T-cell clonal expansion accompanied by the loss of neoantigens suggests the development of an effective immune response," said Dr. Urba. "These data have important implications for understanding the mechanisms of action of checkpoint inhibitors and for the design of future clinical trials."

ADOPTIVE CELL THERAPY

In collaboration with Loyola University, Dr. Curti engaged in a phase I study of adoptive cell therapy, or ACT, in patients with metastatic melanoma. Celebrated as the Advance of the Year by the American Society of Clinical Oncology, ACT harnesses the ability of the immune system to eliminate cancer through the collection, amplification and reinfusion of patients' tumor-killing T cells.

> A significant number of patients experienced regression of their cancers.

The investigators sought to enhance the tumor-killing potency of patients' T cells through T-cell engineering. In the ongoing study, they tested the safety and effectiveness of T cells endowed with a new receptor capable of recognizing tyrosinase, an enzyme present in most melanoma cells. "The future of ACT will involve more sophisticated T-cell engineering," said Dr. Curti. "We are at the forefront of these efforts." Dr. Curti will continue his investigation of novel ACT in partnership with Eric Tran, Ph.D., assistant member, Antitumor T-cell Response Laboratory, whose lab is focused on identifying neoantigens with potential for targeting by ACT.

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Five of 10 publications shown.

Rachel E. Sanborn, M.D., associate member, Phase I Clinical Trials Program, and co-director, Providence Thoracic Oncology Program

Phase I Studies and Lung Cancer

Rachel E. Sanborn, M.D., oversees a robust phase I clinical trials portfolio of experimental cancer immunotherapies, targeted therapies and other novel agents. An expert in thoracic cancers, she leads numerous studies to improve outcomes for patients with lung cancer.

PHASE I STUDY FOR ADVANCED CANCERS

At the 2017 annual meeting of the American Society of Clinical Oncology, Dr. Sanborn gave an oral abstract presentation on a phase I/II study investigating varlilumab, an immune-stimulating antibody, in combination with nivolumab, an anti-PD-1 checkpoint inhibitor approved for several cancers.

Varlilumab targets and binds to CD27, a protein found on the surfaces of T cells, activating an anti-cancer immune response. Investigators hypothesized the combination of varlilumab and nivolumab could have an additive benefit compared to the minimal response expected if patients were given nivolumab only.

The study aims to test the safety and anti-cancer activity of varlilumab in patients with advanced cancers that have resisted prior therapies, including melanoma and cancers of the colon, ovary, head and neck. Of nearly 20 sites participating throughout the country, Dr. Sanborn and colleagues at Providence Cancer Institute were the first investigators to enroll patients to the study.

Reporting preliminary results, Dr. Sanborn noted the combination was well-tolerated, and 14 of 36 patients enrolled to the study saw their tumors shrink

or stabilize in response to therapy. These findings were significant, given the patients' advanced state of disease and poor prognosis.

"Combining PD-1 inhibition with a potent T-cell activating agent provides the opportunity to increase the number of patients that benefit from checkpoint immunotherapy," said Dr. Sanborn. "While early, we have evidence that this combination does not add toxicity and may offer patients clinical benefit, particularly those who are unlikely to respond to other therapies."

Based on the favorable results, investigators will evaluate various dose schedules to determine the optimal treatment regimen.

LUNG CANCER VACCINE PILOT STUDY

While immune checkpoint inhibitors have improved survival of patients with non-small cell lung cancer, or NSCLC, the disease remains the leading cause of cancer death worldwide. Strategies that increase immune recognition and control of NSCLC are needed. Vaccines present a promising approach to priming the immune system to recognize and destroy this deadly malignancy.

In collaboration with Bernard A. Fox, Ph.D., member and Harder Family Chair, Molecular and Tumor Immunology Laboratory, and Hong-Ming Hu, Ph.D., associate member, Cancer Immunobiology Laboratory, Dr. Sanborn conducted a pilot study to test the safety and clinical activity of a novel cancer vaccine in combination with docetaxel, a standard-of-care chemotherapy.

> Combining PD-1 inhibition with a potent T-cell activating agent provides the opportunity to increase the number of patients that benefit from checkpoint immunotherapy.

With support from the National Cancer Institute and the Kuni Foundation, six patients with advanced NSCLC received intravenous infusion of docetaxel, followed by a cancer vaccine derived from their own tumor cells. The autologous vaccine, known as DRibbles, was created by Drs. Hu and Fox by isolating tumor cells from the study patients and processing the cells into a vaccine formulation in the laboratory. In preclinical studies, the vaccine demonstrated both protective and therapeutic anti-cancer immunity.

"The autologous DRibbles vaccine was safe in the small population of patients tested," said Dr. Sanborn. Results were published in the Journal for ImmunoTherapy of Cancer, and further investigation of the DRibbles vaccine has moved forward with an off-the-shelf, or allogeneic, formulation in development for patients with locally advanced NSCLC and other cancers.

INVESTIGATOR-INITIATED LUNG CANCER STUDY

Another study designed for patients with advanced NSCLC, Dr. Sanborn leads an investigator-initiated phase I/II clinical trial of pembrolizumab, another anti-PD-1 checkpoint inhibitor approved for a variety of cancers, in combination with gemcitabine, a standard-of-care chemotherapy.

The study was also selected for presentation by the American Society of Clinical Oncology, where Dr. Sanborn reported a favorable safety profile among six patients. Approximately 16 patients are expected to participate in the trial, which is ongoing through the sponsorship of Providence Health & Services.

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Marka R. Crittenden, M.D., Ph.D., associate member, Integrated Therapies Laboratory, and director, Translational Radiation Research, and **Kristina H. Young, M.D., Ph.D.,** assistant member, Tumor Microenvironment Laboratory

Radiation Research

As physician scientists specializing in radiation oncology and immunotherapy, **Marka R. Crittenden, M.D., Ph.D.**, and **Kristina H. Young, M.D., Ph.D.**, seek to develop more effective treatments for patients with cancer.

INTEGRATING RADIATION AND IMMUNOTHERAPY

Drs. Crittenden and Young are active proponents of incorporating radiation oncology into immunotherapy. As members of the American Society for Radiation Oncology and the Society for Immunotherapy of Cancer, they were invited to attend the 2017 Immunotherapy Workshop, a joint meeting of the societies in collaboration with the National Cancer Institute.

Held in Washington, D.C., the workshop addressed important topics concerning the integration of these cancer therapies. Dr. Crittenden chaired a session on "Rational Combinations of Radiation with Immunotherapy," which included colleagues from Johns Hopkins University, the University of Pennsylvania, and Stanford, while Dr. Young presented preliminary results of her phase II clinical trial testing a novel immunotherapy in combination with chemoradiation in patients with rectal cancer. The study, which includes Dr. Crittenden as a co-investigator, was also selected for presentation by the two societies at their 2017 annual meetings, and at the 2017 Immuno-Oncology Young Investigators' Forum.
Learn more about this study on Pages 4 and 18.

ACT IV GLOBAL STUDY

Glioblastoma is the most common malignant primary brain tumor in adults. While cancers of the brain and

nervous system account for less than two percent of new cancer diagnoses in the United States annually, glioblastoma is an aggressive cancer with poor prognosis: a mere 15 months is the typical length of survival after diagnosis.

Researchers turned to immunotherapy as a potential approach to improve patient outcomes. An expert in radiation and immunotherapy for patients with glioblastoma, Dr. Crittenden engaged in a global, phase III clinical trial testing an experimental immunotherapy in this disease. With 165 centers in 22 countries participating, the randomized, double-blind study known as ACT IV is the most comprehensive of its kind.

Dr. Crittenden and colleagues evaluated the safety and effectiveness of rindopepimut, an investigational cancer vaccine, in combination with temozolomide, a standard-of-care chemotherapy, in patients with newly diagnosed glioblastoma. Rindopepimut targets EGFRvIII, a protein arising from a mutation of the EGFR gene, which is expressed in up to 30 percent of glioblastomas. In previous trials, the vaccine extended patient survival by an average of nine months.

> These results underscore the importance of well-controlled clinical trials in the development of new treatments for cancer.

Of the 745 patients who enrolled, half received rindopepimut and half received a placebo; all patients received temozolomide. Only patients with EGFRvIII-expressing glioblastomas were eligible, and all patients completed surgical resection and conventional chemoradiation prior to entering the study.

As reported in The Lancet Oncology, the investigators found no significant difference between patients who received the placebo and those who received the vaccine. "While disappointing, these results underscore the importance of well-controlled clinical trials in the development of new treatments for cancer," said Dr. Crittenden. Investigators halted the study early, yet numerous clinical trials testing various EGFRvIII-targeting strategies are ongoing in efforts to make progress against this formidable cancer.

RADIOTHERAPY AS IMMUNOTHERAPY

In other research, Dr. Crittenden is examining how the immunological effects of radiation therapy can be enhanced when immune-suppressing forces within the tumor microenvironment are rendered ineffective. In collaboration with Michael J. Gough, Ph.D., associate member, Integrated Therapies Laboratory, she is evaluating the role of a family of three cell-surface receptors, Tyro3, Axl, and Mertk – or TAM, in tumor immune suppression.

Studies show the activity of Axl and Mertk in the tumor microenvironment prevents an effective anti-cancer immune response. Studies also demonstrated the efficacy of radiation in eradicating tumors, and directing anti-cancer immune responses toward residual cancer cells found at the tumor site and throughout the body.

In Emerging Topics in Life Sciences, Drs. Crittenden and Gough report how the potential synergy of radiation therapy with the loss or blockade of these receptors could facilitate immune activation. "Inhibition of the TAM family members is a potent therapeutic strategy to initiate immune responses following radiation-induced cancer cell death," said Dr. Crittenden. *Learn more about the Integrated Therapies Lab on Page 14.*

PUBLICATIONS:

Alice AF et al: Amplifying IFN-gamma signaling in dendritic cells by CD11c-specific loss of SOCS1 increases innate immunity to infection while decreasing adaptive immunity. Journal of Immunology. 2018; 200(1):177-185 [Epub 2017 Nov 17]. PMID: 29150567.

Baird JR et al: STING expression and response to treatment with STING ligands in premalignant and malignant disease. PLoS One. 2017; 12(11):e0187532. PMID: 29135982.

Baird JR et al: Stimulating innate immunity to enhance radiation therapy-induced tumor control. International Journal of Radiation Oncology Biology Physics. 2017; 99(2):362-373. PMID: 28871985.

Patel AA et al. Early HPV-related base of tongue cancer. In: Bell RB, Fernandes RP, Andersen PE, eds. Oral, Head and Neck Oncology and Reconstructive Surgery. China: Elsevier; 2017:649-76.

Sckisel GD et al: Differential phenotypes of memory CD4 and CD8 T cells in the spleen and peripheral tissues following immunostimulatory therapy. Journal for ImmunoTherapy of Cancer. 2017; 5(33). PMID: 28428882.

Tormoen GW et al: The TAM family as a therapeutic target in combination with radiation therapy. Emerging Topics in Life Sciences. 2017; 1(5):493-500.

Weller M et al: Rindopepimut with temozolomide for patients with newly diagnosed, EGFRvIII-expressing glioblastoma (ACT IV): a randomised, double-blind, international phase 3 trial. Lancet Oncology. 2017; 18(10):1373-1385. PMID: 28844499.

STATE-OF-THE-ART SERVICES

With 45,000 square feet dedicated to cancer research, the Earle A. Chiles Research Institute is home to several core facilities, offering our investigators and collaborators the latest in immunological monitoring, flow cytometry, immunohistochemistry, molecular pathology and bioinformatics services.

BIOSPECIMEN REPOSITORY

For more than 20 years, we have maintained a Biospecimen Repository of malignant and benign tissues donated by more than 1,000 patients. Containing more than 60,000 samples, nearly 80 types of cancer are represented from which our scientists perform ongoing, novel research.

IMMUNE MONITORING LABORATORY

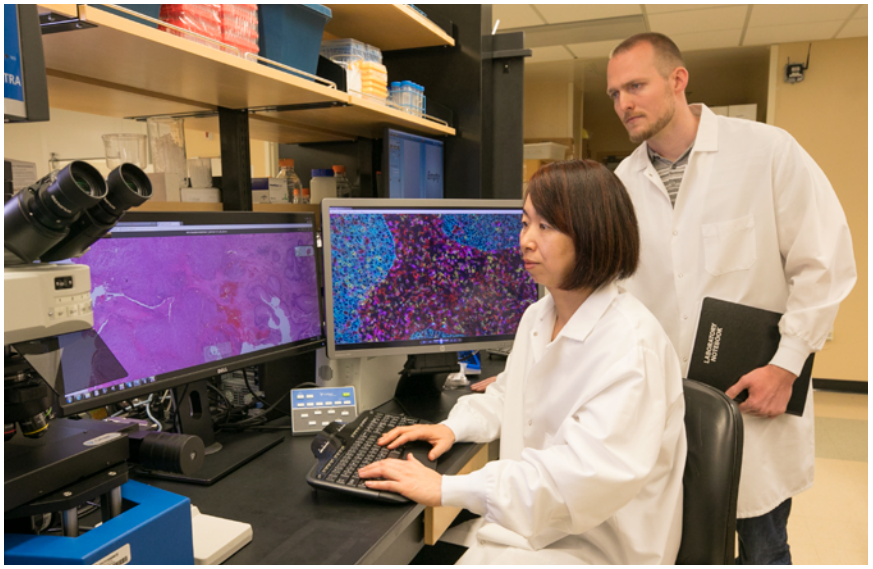
Our Immune Monitoring Laboratory is the archival and disbursement center for the acquisition, processing, cryopreservation and cataloguing of all tumor tissue, peripheral blood mononuclear cells and serum collected during the course of cancer clinical trials. Together with the Flow Cytometry Core, the IML is a national leader in developing and implementing immune monitoring assays for the evaluation of anti-tumor immune responses in cancer patients receiving immunotherapy.

FLOW CYTOMETRY CORE

A heavily used and valuable resource, our Flow Cytometry Core allows investigators to refine their immunotherapy strategies by measuring anti-tumor immune responses on a cellular level. A component of the IML, the core is equipped with a BD Fortessa, BD LSRII, Beckman Coulter Cytoflex, BD FACS Aria II Cell Sorter with BSL2 Containment System, BD FACS Calibur, CTL ImmunoSpot ELISpot, Luminex Bio-Plex 100 and Guava PCA-96, among other instruments.

IMMUNO-HISTOLOGY CORE

Established in 2017 as a component of the IML, the Immuno-Histology Core performs advanced tissue and image analyses in support of our preclinical and clinical studies. It contains a Vectra 3.0 Automated Quantitative Pathology Imaging System; a Zeiss Z1 Motorized Stage Fluorescence Microscope; a Sakura Tissue-Tek, Leica Embedder and RM2235 Rotary Microtome for tissue processing, embedding and sectioning; Ventana Discovery Ultra and Leica auto strainers; and a TMA Master for tissue microarray.



Our newest core facility, the Immuno-Histology Core provides investigators at Providence Cancer Institute with advanced immunohistochemistry services.

MOLECULAR PATHOLOGY CORE

A fundamental component of our translational research, the Molecular Pathology Core provides investigators with molecular correlates to their research questions, enabling the measurement of high-throughput omics projects with clinically validated bioinformatics pipelines. Services include next-generation sequencing of whole exomes and RNA, the analysis and quantification of circulating tumor DNA, mutation analysis with neoantigen prediction and NanoString technology, and T-cell receptor analysis, among other services.

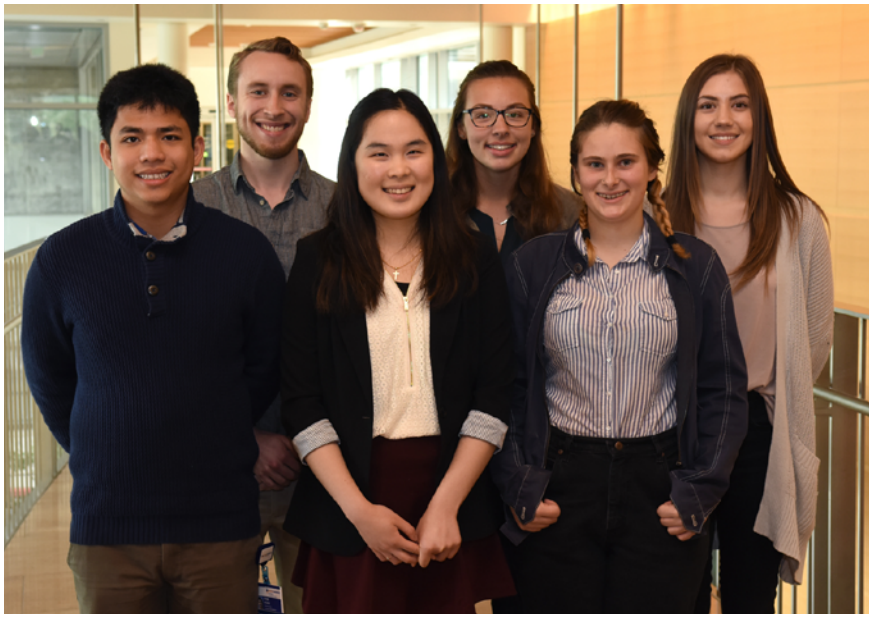
TRAINING PROGRAMS

As part of our mission to train the next generation of immunologists, the Earle A. Chiles Research Institute offers a rich training environment with programs spanning the continuum of higher education, from undergraduates to postdoctoral fellows.

SUMMER RESEARCH PROGRAM. An intensive nine-week internship for undergraduate students, this program provides hands-on research experience and mentorship for students pursuing careers in biomedical sciences. Interns complete an independent research project and present their results at a capstone poster session. They receive training in bioinformatics, and attend research seminars and meetings where recent journal articles are reviewed and discussed. Past interns have been accepted to the Mayo Clinic Graduate School of Biomedical Sciences, Northwestern University School of Medicine and Oregon Health & Science University School of Medicine.

GRADUATE EDUCATION. Through partnerships with OHSU and universities in China, graduate students conduct laboratory research under the guidance of our faculty members with university appointments. Students have opportunities to give poster presentations at national conferences and present their research at department seminars while advancing to doctoral candidacy. Previous students have been accepted to postdoctoral fellowships at the National Cancer Institute, INSERM (French National Institute of Health and Medical Research) and within the biotechnology industry.

POSTDOCTORAL TRAINING. Seeking to acquire the professional skills and experience necessary for independent scientific careers, fellows are mentored in cancer immunotherapy expertise, research skill development, leadership, communication and the responsible conduct of research. The pursuit of external funding and a strong publication record are hallmarks of the program. Previous fellows have received funding from the NIH Pathway to Independence Award, the American Cancer Society, Susan G. Komen and the Prostate Cancer Foundation, and obtained appointments at Rush University, Legacy Research Institute and OHSU.



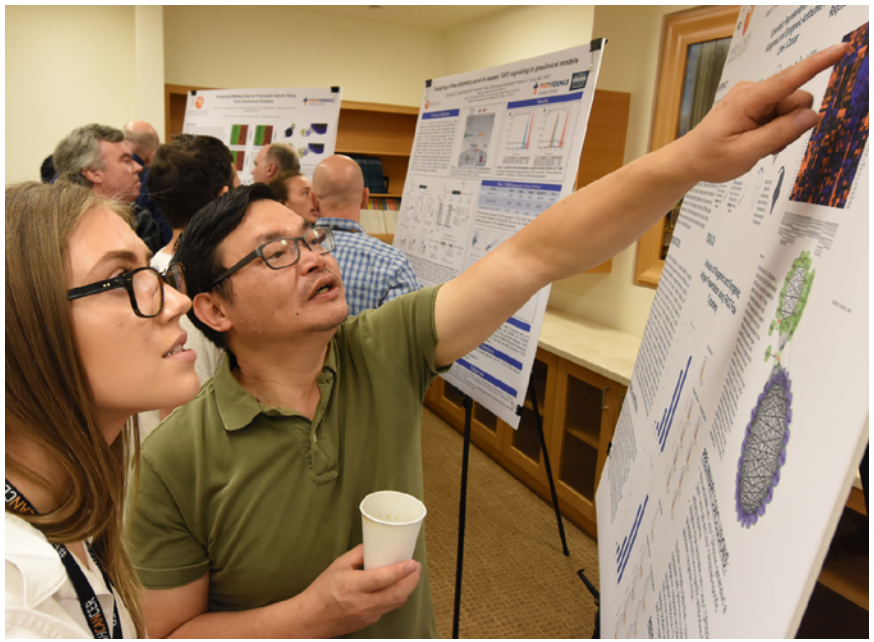


PHOTO ABOVE RIGHT: 2017 Summer Research Program interns. **RIGHT:** Interns present their research projects at a capstone poster session.

BREAKTHROUGH TREATMENTS. TRANSFORMATIVE CARE.

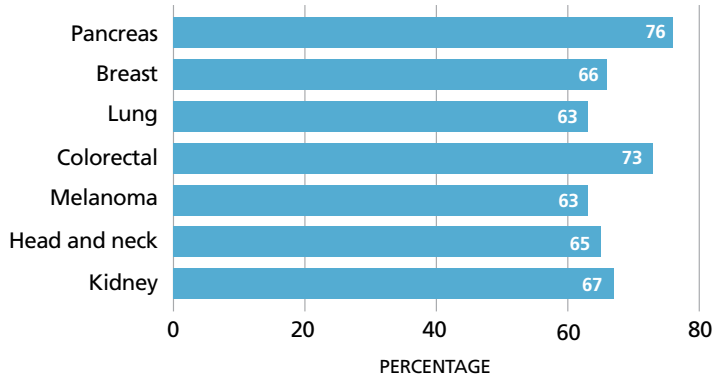
Providence Cancer Institute offers patients the unique advantages of both a world-class cancer research institute and a patient-centered community cancer program. From powerful, breakthrough treatments to compassionate, transformative care and support, we surround patients with everything they need for recovery and healing.

Unmatched experience, more clinical trials, superior outcomes

Studies show that patients do better in centers that treat more people. Our experience supports that:

- Providence Cancer Institute diagnoses and treats more people with cancer than any other health system in the Portland area.

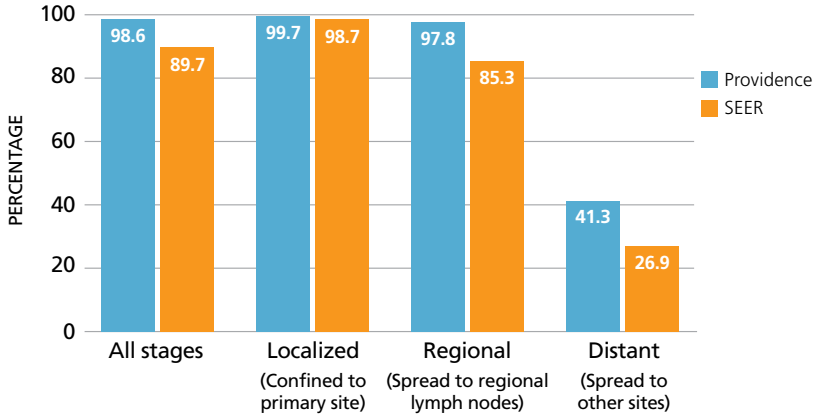
Percentage of Portland cancer patients who received care at Providence



Cancer patients in the Portland area (Multnomah, Clackamas and Washington counties) who received some part of their cancer treatment at Providence Cancer Institute in 2017.

- Survival outcomes for Providence patients surpass the national average.

Five-year relative survival rate: breast cancer



The Providence patient groups include all patients diagnosed with breast cancer from 2008-2014 who received all or part of their initial course of treatment at Providence Cancer Institute. SEER relative survival rates used for comparison are also for patients diagnosed from 2008-2014 and follow-up of patients into 2015. Survival rates have not been adjusted for age, gender, race/ethnicity or insurance status.

- Providence patients have greater access to promising new treatment options.

In 2017, more than **245 cancer research studies** were open to our patients, including 170 therapeutic clinical trials and 48 phase I trials. More than **30 percent** of our adult patients participated in cancer research studies, **compared to 2 to 4 percent** nationally.

Compassionate support

In addition to powerful cancer therapies, we offer supportive care for the body, mind and spirit. Providence patients have access to:

- Nurse navigators to guide them through their experiences
- Integrative care: acupuncture, naturopathy and massage therapy
- Social work services, including 1:1 counseling and in-person or online English and Spanish support groups
- Nutrition advice from registered oncology dietitians
- Palliative care
- Financial counseling
- Extensive resources online at ProvidenceOregon.org/cancersupport

In 2017, we also produced a new series of videos to provide patients with practical advice for coping with the common side effects of cancer and its treatment. The videos feature Providence patients and providers, and can be seen at ProvidenceOregon.org/livingwellvideos.

Prevention and outreach

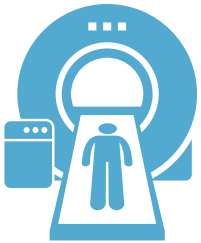
Providence Cancer Institute provided **cancer screenings** to hundreds of Oregonians in 2017 through outreach programs aimed at detecting cancer in the earliest stages, when it is most treatable.

Lung cancer screenings:

678 new patients screened

1,430 total scans

28 cancers found



599 head and neck cancer screenings

160 skin cancer screenings

We also helped raise cancer awareness throughout the state by hosting and participating in **33 community events** in 2017.

Learn more about our clinics, services and events at ProvidenceOregon.org/cancer.

Robert W. Franz Cancer Center named to honor Oregon philanthropist

A Portland native, Robert W. "Bob" Franz became a passionate supporter of research to end cancer in 1986 when he joined the board of Providence Portland Medical Foundation. His intense curiosity, generosity and leadership played a major role in launching and furthering cancer research efforts at Providence Portland Medical Center, the future home of Providence Cancer Center.

EARLY SUPPORTER

Bob and his sister Elsie Franz Finley were early supporters of Providence Cancer Center and its trailblazing successes in the field of immunotherapy. Together, Bob and Elsie quietly and consistently ensured Providence researchers had the resources they needed to become international leaders in immunotherapy for patients with cancer.

Immunotherapy boosts the body's own defenses against cancer by activating the immune system to find and destroy tumors. This approach has been shown to be effective in several types of advanced cancers, including lung, bladder, lymphoma and kidney cancers, as well as melanoma.

TRANSFORMATIONAL PHILANTHROPIST

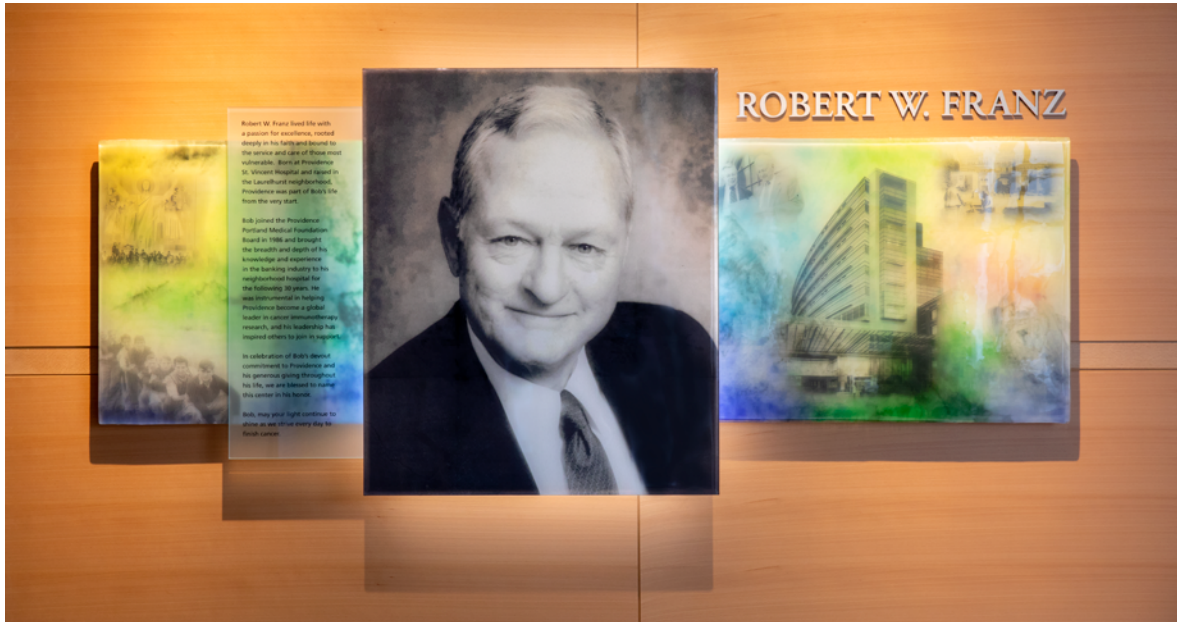
With a lifetime of philanthropic support for cancer research, Bob's total giving to Providence Portland Medical Foundation – $40 million – makes him the single largest donor in Providence's 142 years in Oregon.

Bob died in August 2016 and as a fitting and lasting tribute to him and his legacy of contributions, Providence Cancer Center – the 11-story tower that houses cancer research and services – was renamed in his honor in October 2017. The facility is now the Robert W. Franz Cancer Center, part of Providence Cancer Institute.

> With the support of Providence and people like Bob, our team is well-positioned to show just how potent immunotherapy can be in the treatment of cancer.

The Franz estate gift will be used to attract more top researchers from around the world, build new laboratory and research space, and speed progress toward Providence's overarching goal to finish cancer in our lifetimes.

"Bob's gift is transformative," said Walter J. Urba, M.D., Ph.D., member, director and endowed chair of Cancer Research at the Earle A. Chiles Research Institute, the research arm of the Robert W. Franz Cancer Center. "It allows us to think about the future in ways we never have before. With the support of Providence and people like Bob, our team is well-positioned to show just how potent immunotherapy can be in the treatment of cancer."



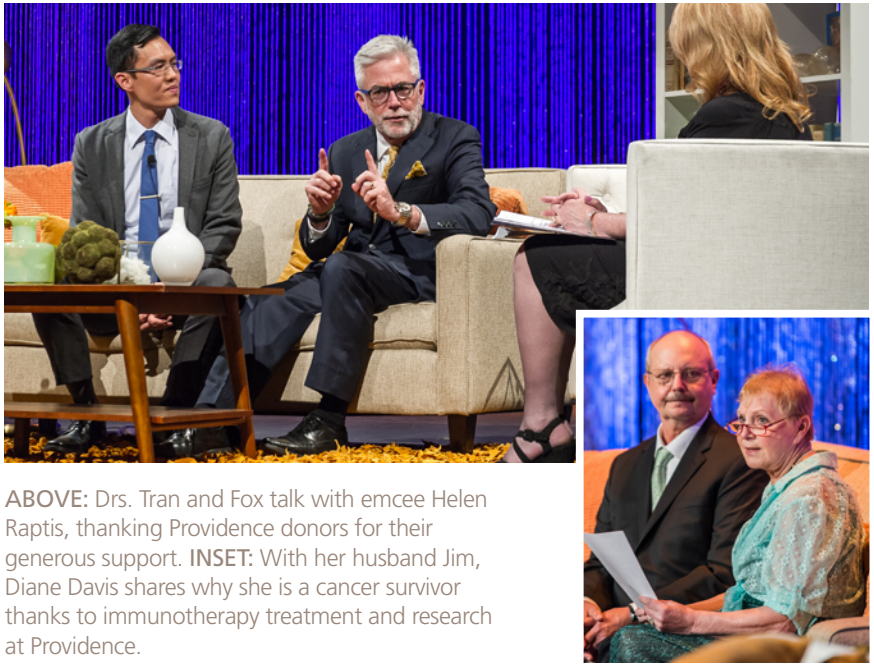
A commemorative plaque depicting the transformational philanthropy of Robert W. Franz greets patients and guests entering the cancer center named in his honor.

Creating Hope

Research creates new treatments and new treatments create hope. That was the message to the more than 500 supporters of Providence Cancer Institute who attended the Providence Creating Hope Dinner on May 24, 2017.

The 19th annual Creating Hope dinner broke records, raising more than $778,000 in support of cancer research. Coupled with contributions from Safeway customers and employees throughout the month of May, more than $1 million was raised for translational cancer research.

The signature fundraising event for cancer research featured Diane Davis, a survivor of ovarian cancer thanks to lifesaving immunotherapy she received as part of a first-in-human clinical trial at Providence. Guests also heard from Bernard A. Fox, Ph.D., and Eric Tran, Ph.D., faculty members of the Earle A. Chiles Research Institute, on the importance of philanthropy in advancing treatments for cancer patients.



ABOVE: Drs. Tran and Fox talk with emcee Helen Raptis, thanking Providence donors for their generous support. **INSET:** With her husband Jim, Diane Davis shares why she is a cancer survivor thanks to immunotherapy treatment and research at Providence.

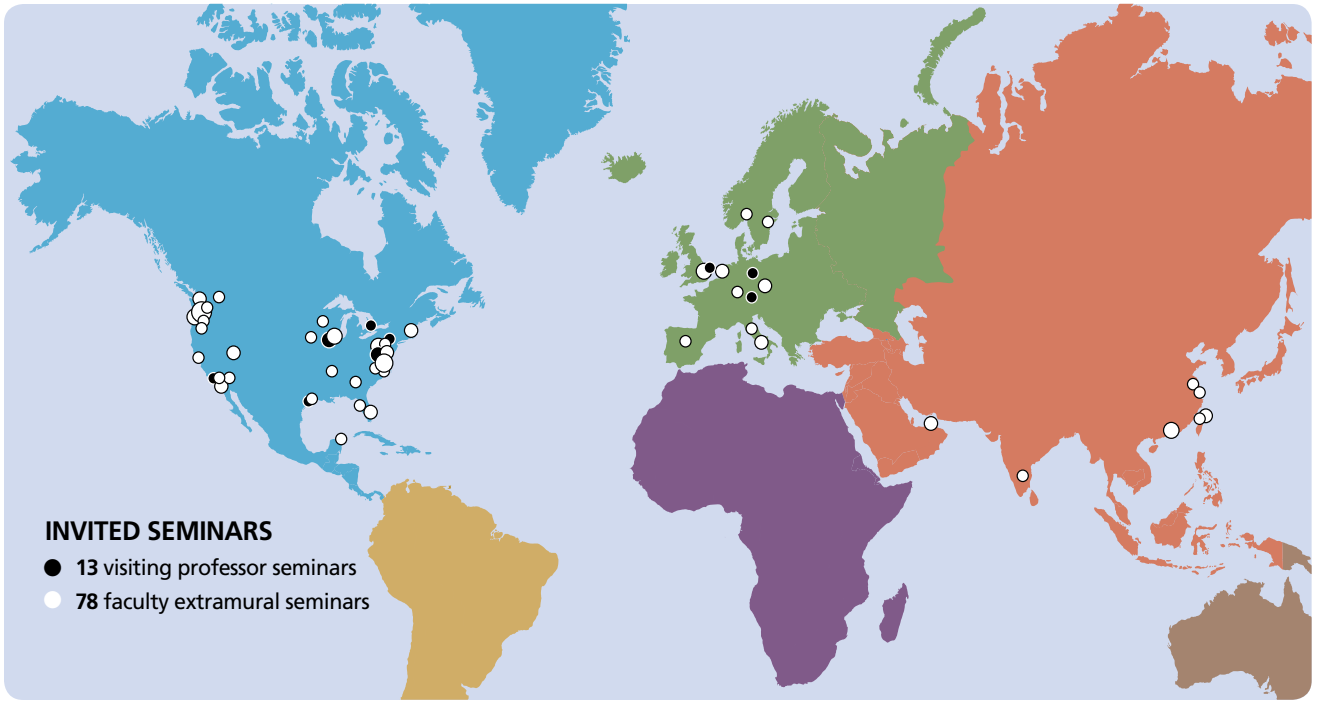
Team Runners4Research includes Providence Cancer Institute scientists, nurses, doctors and friends.

Hood to Coast

The 2017 Providence Hood to Coast Relay was a huge success, raising more than $740,000 for cancer research at Providence. This is the fifth year the relay has been a major fundraiser for Providence. Teams that fundraise are guaranteed one of the coveted spots in the race. The top fundraising team for 2017 was All In, No Regrets. They raised $42,495 for cancer research.

More than 1,000 running teams participated in the 199-mile race from Mt. Hood to the coastal town of Seaside, Oregon. An additional 400 walking teams and 50 high school teams covered the 130-mile Portland to Coast Relay.

BY THE NUMBERS: 2017 FACTS AND FIGURES



Memberships & Collaborations

- Bristol Myers-Squibb International Immuno-Oncology Network
- NCI Community Oncology Research Program via Pacific Cancer Research Consortium
- NCI Cancer Immunotherapy Trials Network
- Partnership with MedImmune/ AstraZeneca for clinical development of anti-OX40

Investigators & Personnel

19 faculty members

49 clinical researchers

63 lab researchers

Institute Publications

142 total publications:

53 journal articles

10 books and book chapters

79 conference abstracts

Grant Funding, Sponsored Research & Philanthropy

$4.5 million annually in federal, private and sponsored research funding

$32.5 million raised by Providence Foundations in Oregon for Providence Cancer Institute

Clinical Trials

246 cancer clinical trials open for enrollment, including **170** therapeutic trials and **48** phase I trials

1,798 total enrollments

Faculty Members

R. Bryan Bell, M.D., D.D.S., FACS
Assistant member and medical director,
Providence Head and Neck Cancer Program and Clinic
Head and Neck Oncologic Surgery

Carlo B. Bifulco, M.D.
Member and director,
Translational Molecular Pathology
Medical director, Molecular Genomics
Anatomic and Molecular Pathology

Alison K. Conlin, M.D., MPH
Associate member and medical director,
Providence Breast Cancer Medical Program and High-Risk Breast Clinic
Medical Oncology

Marka R. Crittenden, M.D., Ph.D.
Associate member,
Integrated Therapies Laboratory
Director, Translational Radiation Research
Radiation Oncology

Todd S. Crocenzi, M.D.
Associate member and director,
Gastrointestinal Oncology Research
Medical Oncology

Brendan D. Curti, M.D.
Member and director,
Cytokine and Adoptive Immunotherapy Program, Genitourinary Oncology Research and Providence Melanoma Program
Medical Oncology

Bernard A. Fox, Ph.D.
Member and Harder Family Endowed Chair for Cancer Research, Molecular and Tumor Immunology Laboratory

John E. Godwin, M.D., MS
Member and program leader,
Hematologic Malignancies
Medical Oncology

Michael J. Gough, Ph.D.
Associate member,
Integrated Therapies Laboratory

Hong-Ming Hu, Ph.D.
Associate member,
Cancer Immunobiology Laboratory

Rom S. Leidner, M.D.
Assistant member and co-director,
Providence Head and Neck Cancer Program
Medical Oncology

Philippa H. Newell, M.D.
Assistant member and medical director,
Providence Liver Cancer Clinic
Liver and Pancreas Surgery

David B. Page, M.D.
Assistant member,
Breast Cancer Immunotherapy
Medical Oncology

William L. Redmond, Ph.D.
Associate member,
Cancer Immunotherapy Laboratory
Director, Immune Monitoring Laboratory

Rachel E. Sanborn, M.D.
Associate member,
Phase I Clinical Trials Program
Co-director, Providence Thoracic Oncology Program
Medical Oncology

Eric Tran, Ph.D.
Assistant member,
Antitumor T-cell Response Laboratory

Walter J. Urba, M.D., Ph.D.
Member, director and endowed chair of Cancer Research
Medical Oncology

Andrew D. Weinberg, Ph.D.
Member and Judith Ann Hartmann Endowed Chair for the Laboratory of Basic Immunology

Kristina H. Young, M.D., Ph.D.
Assistant member,
Tumor Microenvironment Laboratory
Radiation Oncology

Administration

Julie Cramer, MA, CCRP
Administrative director,
Cancer Clinical Research

Samantha Kaiser
Director, Cancer Research Operations

Franz Leadership Cabinet

The Robert W. Franz Cancer Leadership Cabinet comprises men and women with a desire to connect the Portland metropolitan community with the dedicated teams of researchers working to finish cancer at the Earle A. Chiles Research Institute. Founded in 2001, the leadership cabinet has a strong and loyal membership representing a broad spectrum of the community.

2017 CABINET MEMBERS

TJ O'Connor, chair
Flo Atkinson
Stephen Bader, M.D.
Mark Beckius
Walter C. Bowen
Kay Carlisle
Charlie Engelberg
Dan Floyd
Pedro Garcia
Diana Hall
Cindy Harder
Dan Kinney
Sheryl Langerman Rosenfeld
Lynn Loacker
Patricia Markesino
Nicole McIntyre
Jooyon K. "Julieann" Park
Linda Read
James F. Robb, Ph.D.
Linda Smiley
Mark Williams
Linda Yoshida

OUR MISSION
As expressions of God's healing love, witnessed through the ministry of Jesus, we are steadfast in serving all, especially those who are poor and vulnerable.

OUR VALUES
Compassion, Dignity, Justice
Excellence, Integrity

chilesresearch.org

PROVIDENCE
Cancer Institute